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## Original Communications

### PROTAMINE INSULIN: ITS USE IN CHILDREN


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THE management of diabetes mellitus in the child is influenced by problems of growth and education. These problems, combined with the realization that the severity of the disease is frequently greater than in adults, make a strict regime imperative. Any lessening of the load carried by diabetic children and their parents would be welcomed provided satisfactory control of their diabetes could be assured. Insulin with protamine appears to offer such a possibility and at the same time, in certain patients, maintains a better control of the hyperglycemia than regular insulin.

Since March, 1936, we have used protamine insulin* in the treatment of thirty-two patients with juvenile diabetes mellitus both in the hospital and out-patient department. Fourteen of the thirty-two children have had from two to six weeks' study in the Children's Memorial Hospital. The diets were essentially unaltered in the hospital patients with the change to protamine insulin, although in a few instances redistribution of the carbohydrate between the three meals was found advantageous. Meals were served at 8 A.M., 12 M., and 6 P.M.; blood sugar determinations were made at 6:30 A.M., 11 A.M., 2 P.M., 5 P.M., and 11 P.M., on capillary blood by a modified Folin-Wu method.[1] Over 2,000 blood sugar determinations were made in this study. Urinary sugar estimations were made on six-hour specimens by Benedict's method. Observations of the effect of varied schedules and types of protamine insulin were carried out.

1. *Protamine Insulin (Plain) Substituted for Regular Insulin Before Meals.*—In a preliminary group of patients protamine insulin was substituted for the regular insulin prior to each meal, the doses remaining the same. In two severely diabetic patients of this group, control of

From the Children's Memorial Hospital, Dr. Joseph Brennemann, Chief of Staff.
*Supplied by the Eli Lilly Co., courtesy Dr. F. B. Peck.

the 11 P.M. blood sugar level was less successful than with regular insulin, but good results were generally shown in a reduction of the fasting blood sugar to low normal levels. The partial failure in these patients may be attributed to the fact that the carbohydrate of the evening meal was not reduced. Hagedorn and his coworkers[2] obtained the best results when the available glucose of the evening meal was reduced to 20 per cent of that of the entire diet. Two mildly diabetic patients in our first group were well controlled by protamine insulin given before breakfast and the evening meal with no change in the carbohydrate distribution.

A boy seven and one-half years old had diabetes for eight months, and the urine was sugar-free with morning and evening doses of 5

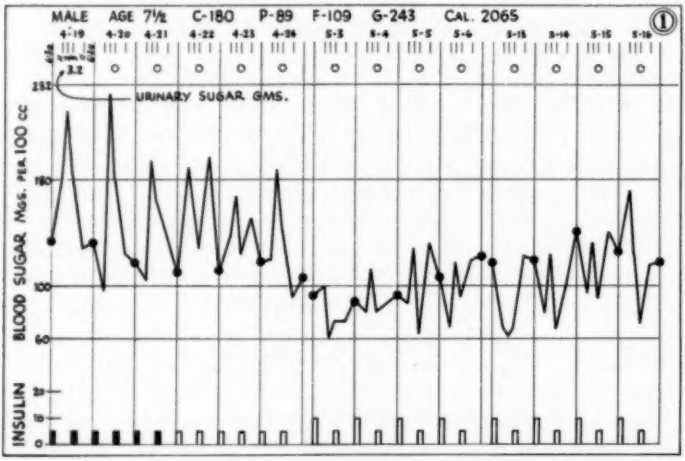


Chart 1.—The large black dots represent the fasting blood sugar. Regular insulin is indicated by black columns, protamine insulin by clear columns. Improvement is noted when insulin-P was started, great improvement when the morning dose was increased to 10 units. Since discharge from the clinic, glycosuria is rarely noted on one morning dose of 15 units of insulin-P.

units of insulin-R (Chart 1). Insulin-P was substituted in equal doses at the same meals. Hyperglycemia was better controlled under the new treatment, and the blood sugar fell to a very low level when the morning dose was increased to 10 units. Later, upon discharge from the hospital, one morning dose only of 12 to 15 units of insulin-P was prescribed. Glycosuria of a mild degree has occurred infrequently. This patient has been less hungry and requested a reduction in diet. Recently he has asked for more food but has not been abnormally hungry.

A twelve-year-old boy who had diabetes for nine months had been sugar-free on two daily doses of insulin-R, 15 units in the morning and 10 units at night (Chart 2). Insulin-P was substituted for both doses

of insulin-R. Rapid control of the fasting blood sugar was established after two days, the hyperglycemia after four days. It appeared that, after the return to insulin-R, the insulin-P continued to be active for several days, for the 5 P.M. blood sugar level fell to a point below its

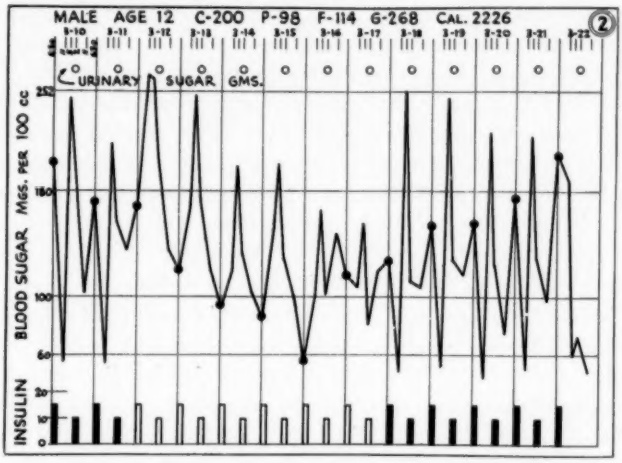


Chart 2.—Rapid control of the fasting blood sugar after four days' control of hyperglycemia. After withdrawal of insulin-P, the low level of the 5 P.M. blood sugar (112-128) points to the persisting effect of insulin-P.

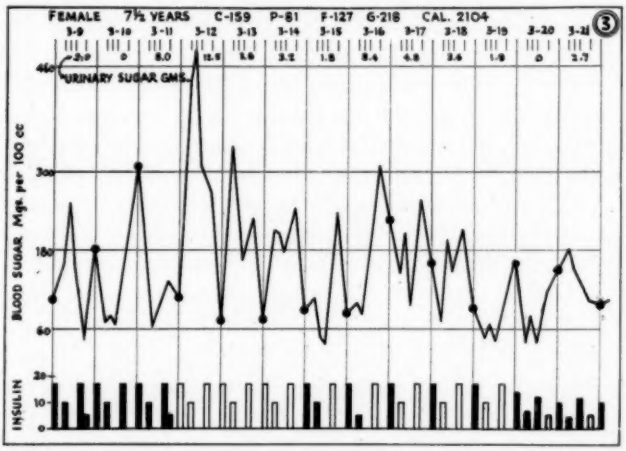
FEMALE 7½ YEARS C-159 P-81 F-127 G-218 CAL. 2104
3
3-9 3-10 3-11 3-12 3-13 3-14 3-15 3-16 3-17 3-18 3-19 3-20 3-21
URINARY SUGAR GMS.
BLOOD SUGAR Mgs. per 100 cc
INSULIN

Chart 3.—Good control of the fasting blood sugar, demonstrating the slow action of insulin-P with a resultant hyperglycemia at 11 A.M. The 11 P.M. blood sugar was frequently elevated above normal range.

subsequent levels during those days. Since discharge from the hospital, glycosuria of a mild degree has been noted occasionally. This boy was definitely less hungry during the period when insulin-P was administered.

2. *Protamine Insulin (Plain) Replacing the Evening Dose of Regular Insulin.*—This schedule was outlined by Root and his associates[4] and Kerr and his coworkers.[5]

In a seven-and-one-half-year-old girl who had diabetes for eighteen months, the disease had been well controlled for the first year with 14 to 16 units of insulin-R, but had been poorly controlled during the past winter (Chart 3). The hyperglycemia was controlled by four doses of insulin-R daily, but marked improvement over the earlier fasting blood sugar level was noted when the evening and the midnight doses of insulin-P were substituted. Since in this patient multiple doses of either substance were required, there was no advantage in using insulin-P except that in general normal fasting blood sugar values were obtained. In this patient the condition is now well controlled with 30 to 32 units of zinc protamine insulin.

3. *Simultaneous Doses of Regular Insulin and Protamine Insulin (Plain) Before Breakfast.*—This schedule was recommended by Sprague and his coworkers.[6] The regular and protamine insulins were injected in different sites.

A six-and-one-half-year-old boy who had diabetes for four years had usually been sugar-free before the evening meal, rarely before breakfast, with two doses of insulin-R totaling 30 to 40 units daily (Chart 4). Having found that the hyperglycemia could be controlled by four daily doses of insulin-R, we prescribed the matutinal dose of insulin-R plus insulin-P in an amount equal to the sum of the three other doses of insulin-R. With further adjustments of the insulin moderately good control of the hyperglycemia was observed with one dose of insulin-P. At a later period, with the development of an acute respiratory infection, two morning doses again became necessary to secure fairly good control. This patient experienced minor hypoglycemic reactions, but all were readily managed with glucose orally. After discharge from the hospital on a dosage of 10 units of insulin-R and 30 units of insulin-P, this patient returned with a normal fasting urine. There had been several mild reactions at home, few with protamine alone. Some glycosuria was present on 24-28 units of zinc protamine insulin.

As is shown by the accompanying charts, several days must elapse before the hyperglycemia is under control. It is felt by the Mayo workers that this slow effect is due to the cumulative action of insulin-P, since in one patient the hypoglycemic effect persisted for thirty-nine hours after a meal. Lawrence and Archer[7] found under similar conditions, but with a carbohydrate-free diet, that the duration of action was as long as fifty-five hours. Their patient developed an acidosis which they believed was a result of the storage of all the available endogenous glucose as glycogen.

The success with protamine as a precipitant of insulin has stimulated search for other precipitants. Gray[8] has recently reported comparable results with a tannic acid solution. Protamine insulin stabilized with zinc and calcium chloride has also been advocated by Fisher and Scott.[9] A similar prolongation of insulin effect was recorded on the addition of zinc to two newly isolated substances—spermine from pancreas and a preparation from beef thymus glands.[9]

The calcium and zinc preparations have recently been supplied to us. One milligram of calcium was added to each 100 units of insulin, 1 mg. of zinc to each 500 units of insulin. The following record is a typical example of one of four children receiving the calcium preparation: A six-and-one-half-year-old girl who had diabetes for four years

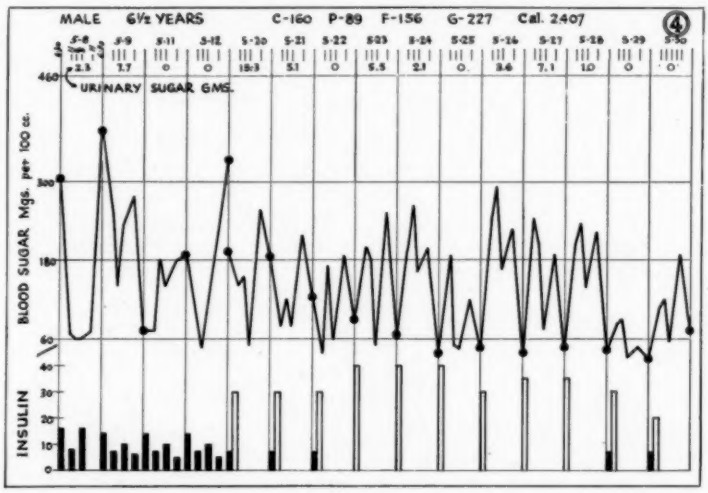


Chart 4.—Fairly good control of hyperglycemia with four doses of insulin-R totaling 36 units. In the second section improved control with 35 to 40 units of insulin-P only producing a constant low fasting blood sugar. Good control was finally established with 7 units of insulin-R and 20 units of insulin-P except for interruption on account of an upper respiratory infection with fever.

had been partially controlled with 20 to 28 units of insulin-R (Chart 5). There was failure to control the glycosuria and hyperglycemia with 44 units of calcium protamine insulin and with 18 units of insulin-R and 38 units of calcium protamine insulin. The fasting blood sugar was usually within normal range. Zinc protamine insulin appeared to produce more adequate control with low morning blood sugars and daily reactions. With return to the calcium preparation and reduction in the dose because of reactions, there was loss of control partially because of inadequate dosage as indicated by the high fasting blood sugar. The glycosuria was fairly well controlled in the home with one dose of 28 units of zinc protamine insulin. She was more irritable than formerly.

The results in the hospital obtained with the zinc protamine insulin were the most satisfactory of the three preparations. Control of hyperglycemia was more rapid and more nearly perfect, especially when a portion of the evening carbohydrate was transferred to the morning meal. The two following cases illustrate our results with the zinc

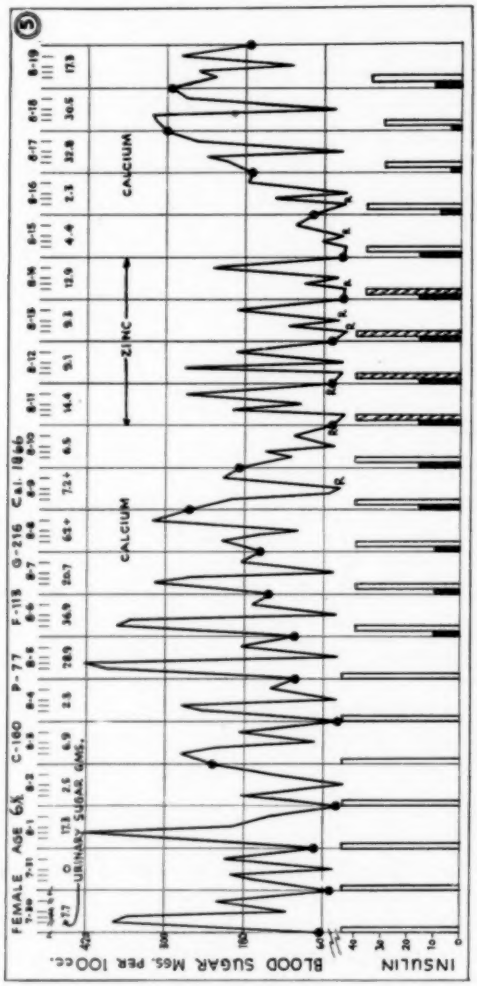


Chart 5.—Failure to control hyperglycemia and glycosuria with doses of 44 units of calcium protamine insulin. Somewhat better control is demonstrated with zinc protamine insulin.

preparation: A twelve-and-one-half-year-old girl who had diabetes for four years had been sugar-free for the first two years with 10 units of insulin daily (Chart 6). With the development of a thyroid enlargement and an increased metabolic rate, the insulin requirement very rapidly rose to 60 units daily, although the glucose of the diet

had been increased only 15 gm. A year later the glucose of the diet was increased 40 gm. Recently, the basal rate fell to normal levels, and the insulin requirement fell to 36 units daily. Adequate control of this patient's diabetes was rapidly secured with matutinal doses of zinc protamine insulin and insulin-R. The carbohydrate of the evening meal was later reduced to about 20 per cent of the total daily amount, and the disease is now well controlled at home with 15 units of insulin-R and 25 units of zinc protamine insulin.

A ten-and-one-half-year-old boy who had diabetes for one year and had been well controlled with 16 to 32 units of insulin-R (Chart 7). The glucose of the diet was about equally distributed between the three meals. The 11 P.M. and the fasting blood sugar levels were found

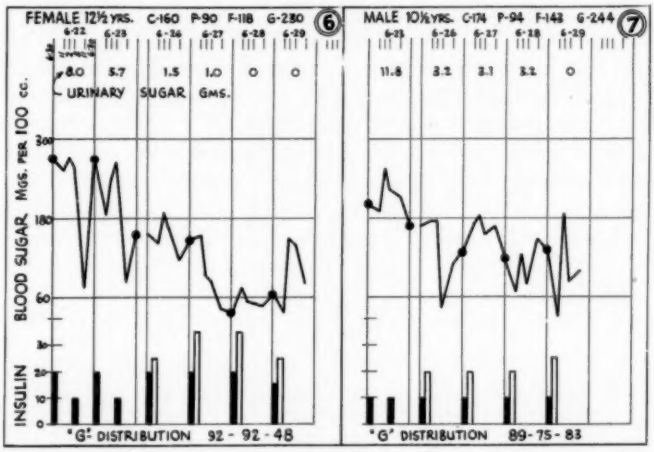


Chart 6.—Excellent control of hyperglycemia with zinc protamine insulin. Carbohydrate of evening meal reduced to one-fifth of total daily intake.

Chart 7.—Good control of hyperglycemia without change in the distribution of carbohydrate. Now well controlled at home with one dose only of 20 to 22 units of protamine zinc insulin alone.

to be within normal limits but were higher than those of the preceding patient. After discharge from the hospital he was sugar-free with 30 units of zinc protamine insulin plus 7 units of insulin-R and for the past three months has been well controlled with 20 to 22 units of insulin-P alone.

## DIETS

The diets have been relatively high in carbohydrate, averaging 6 gm. per kilogram, the highest being 9. Protein content has been quite high because of the need of stimulating growth particularly in the smaller children, averaging 3½ gm. per kilogram, the highest being 5 gm. per kilogram. The fat content was relatively low, averaging 4 gm. per kilogram, the highest being 7 gm. per kilogram.

The daily diet prescription was unchanged during the hospital stay, but the prescription for the individual meals was altered especially when one dose of protamine alone was administered.

*After discharge from the hospital*, early morning hypoglycemic reactions often occurred with protamine insulin alone until additional carbohydrate was added to the evening meal. Glycosuria was often noted at noon unless the carbohydrate of the breakfast was reduced. In fact, it has been our procedure recently to take a portion of the carbohydrate from breakfast and add equally to the noon and evening meals. In some instances, because of the morning hypoglycemia, additional carbohydrate was sometimes prescribed at the evening meal.

### HYPOGLYCEMIC REACTIONS

Reactions from overdosage of protamine insulin appear more slowly and usually at a lower level of the blood sugar. Because of the retarded and prolonged effect, more glucose must be administered in the treatment of insulin shock. Recurrent reactions are more frequent because of this prolonged effect. The parent must be instructed thoroughly in the likelihood of these persistent and recurrent reactions.

Insulin reactions have occurred very frequently in our experience after discharge from the hospital, particularly if there has been no readjustment of the carbohydrate of the meals, if the patient fails to eat his entire diet, or if large doses of both fast and slow acting insulin are prescribed.

### COMMENT

During the first few days after the change from regular to protamine insulin, a greater glycosuria was not infrequent, possibly due to a delayed absorption of part of the insulin for more than twenty-four hours. This was less marked when changing to zinc protamine insulin in cases in which the control seemed to be more rapid. Ketosis developed in one patient: an infant treated for a few days in the home; in this case other factors were felt to be responsible. No instance of allergic manifestation or local reactions was seen.

Increased irritability was observed in two children, in one in whom the disease was well controlled and in the other in whom it was poorly controlled. The mother was displeased in one instance because her boy was getting thin and had failed to gain for the past two months. It was interesting that this patient had gained over two inches in five months, and that the liver had definitely decreased in size.[10] These two changes were observed in two other small boys.

However, many of the patients were greatly pleased that they had not experienced periods of intense hunger as they did while receiving insulin-R. In general, the mothers report more activity and alertness. In instances in which all the insulin could be administered in the morning, the children were happier and more stable emotionally. In

23 out of 32 cases studied, satisfactory control was obtained by a single morning dose. The afternoon and evening activities did not need to be so carefully restricted; this was most agreeable to both parents and children.

During the summer there was a definite decrease in the total dosage of protamine insulin, but after the children returned to school, an increase of insulin was indicated. In some instances, there has been an apparent increase in tolerance while other patients required more protamine insulin than regular insulin.

## CONCLUSIONS

From this study of 14 hospital patients and 18 out-patients, the following conclusions have been drawn:

1. Patients with mild juvenile diabetes can be treated with a single morning dose of protamine insulin, and good control of the diabetes can be secured.

2. Simultaneous matutinal administration of a large dose of protamine insulin and a small dose of regular insulin will control a majority of the patients with severe diabetes.

3. An adequate evening or midnight dose of protamine insulin will produce a normal fasting blood sugar.

4. Protamine calcium insulin failed to produce adequate control of glycosuria and hyperglycemia.

5. Protamine zinc insulin produced a normal midnight and a fasting blood sugar level in a shorter period of time than plain protamine insulin.

6. In general, the mothers reported that the children did not experience the periods of intense hunger, that they were more active and alert, and in the cases that received all the insulin in the morning the children were happier and more stable emotionally. Twenty-three of thirty-two patients are now receiving one matutinal dose only of protamine insulin.

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707 FULLERTON AVENUE

# CLINICAL EXPERIENCE WITH PROTAMINE AND CRYSTALLINE INSULIN IN THE TREATMENT OF DIABETES MELLITUS IN CHILDREN

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SINCE the introduction of protamine insulin by Hagedorn,[1] there have been numerous reports concerning its clinical use which have substantiated the early claims that the action of protamine insulin is less rapid but more prolonged than that of regular insulin. Hagedorn stated that protamine insulin, after injection, was active for from twelve to fourteen hours, or approximately twice as long as regular insulin. He advised the use of protamine insulin for the evening injection and regular insulin in the morning and, if necessary, at noon. By this method the fasting blood sugar in the morning was maintained within reasonable limits in contrast to the usual high blood sugar in diabetic children when regular insulin is given at the time of the evening meal. From the work of Lawrence[2] it appears that there might be a relation between the size of the dose of protamine insulin and the length of its action; the larger the dose the more prolonged the effect. In fact, in one instance, Lawrence observed a prolongation of the action for fifty-five hours after the injection of 120 units of protamine insulin, when the patient was given a diet consisting of fat and protein. Wilder and his associates[3] kept a diabetic patient in a state of hypoglycemia from the ninth to the thirty-ninth hour after injection of protamine insulin. This patient received no food after injection until the thirty-ninth hour, when the hypoglycemia was corrected. These authors made a distinct contribution when they showed that some diabetics may be kept in satisfactory glycemic equilibrium by a single dose of protamine insulin given before breakfast. They did suggest, however, that in some instances a supplementary injection of regular insulin at the same time might be desirable. More recently in view of the work of Scott and Fisher,[4] zinc has been added to the protamine, producing a compound with an even more prolonged action. For a short period of time protamine calcium insulin was supplied for clinical trial. This product has been discontinued. Our experience has been successively with protamine insulin, protamine

From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati.

A portion of the data was secured at the Camp for Diabetic Children, Glendale, Ohio. This camp was made possible in the summer of 1936 by a small group of Cincinnati citizens and was operated under the direction of the staff of the Children's Hospital.

calcium insulin, and protamine zinc insulin. Protamine zinc insulin was employed in all of the children reported here.*

An example of satisfactory results from a single injection of protamine insulin is shown in Chart 1. The marked difference between the effect upon the blood sugar of the following morning of equal doses of protamine insulin and of regular insulin given at supper time is shown in this chart as well as in most of the others. We have found that it is particularly advantageous when beginning the use of protamine insulin to administer the first dose in the evening and to continue thereafter with the regular morning injection. By this method the blood sugar of the morning is usually within the normal range and the slowly acting protamine does not have to overcome the additional

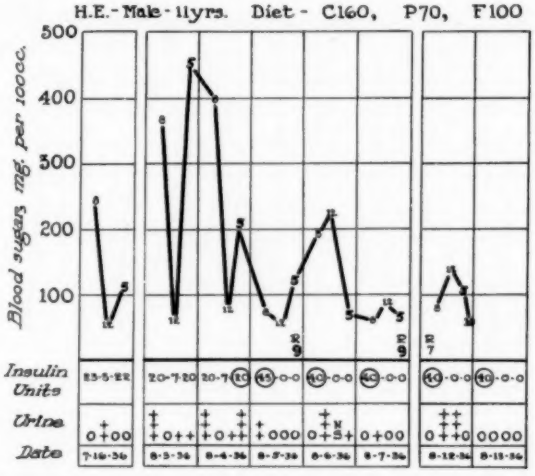


Chart 1.—Satisfactory results from one injection of protamine zinc insulin per day.

Key to Charts:

Graph: The figures indicate the hour at which blood samples were collected, light face numerals represent A.M. and dark face P.M. "R" signifies insulin shock; the numeral the hour of occurrence.

Insulin: Plain numerals represent units of regular insulin; numerals enclosed in a circle, protamine insulin; and those in a square, crystalline insulin.

Urine, qualitative Benedict tests: 0 = blue, + = green, $\frac{+}{+}$ = greenish yellow to yellow, and $\frac{+}{+}$ = orange through red.

In Charts 1, 2, and 6, the urine was collected at 8:00 A.M., 12 noon, 5:00 P.M. and 9:00 P.M., and in Charts 3, 4, 5, 7, 8, and 9 at 8:00 A.M., 11:00 A.M., 4:00 P.M, and 8:00 P.M.

All blood examinations were made on capillary blood.

burden of an existing hyperglycemia (for contrast see Chart 4). Our practice has been to establish reasonably satisfactory glycemic equilibrium with regular insulin, then to administer the same number of units of protamine before the evening meal as had been given of regular insulin at this time. The following morning an injection of pro-

*The various protamine products were supplied through the courtesy of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

tamine insulin consisting of approximately the total daily requirements of regular insulin is given before breakfast according to the plan suggested by Wilder. Subsequent adjustments in dosage are made in accordance with the level of the blood sugar and the amount of urinary sugar.

In general, we have not been able to maintain satisfactory glycemic balance by the administration of a single dose of protamine insulin in the morning. If an amount is given which is sufficient to lower adequately the level of the blood sugar after the noon and evening meals, the patient is quite likely to have a hypoglycemic shock during the night or early morning hours. On the other hand, if the amount of protamine is adjusted so that the blood sugar level of the following

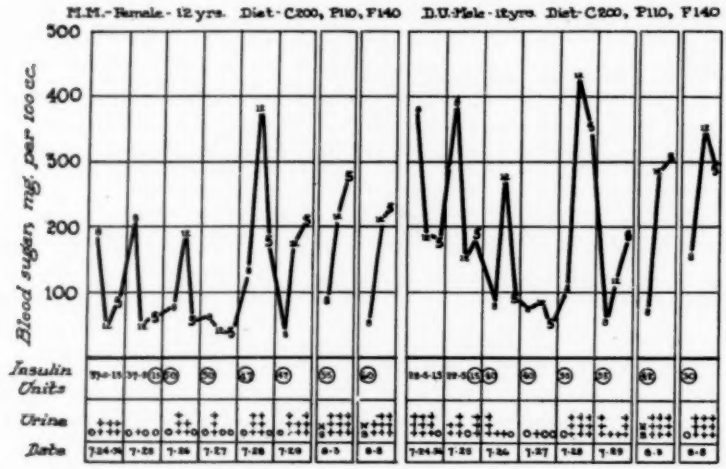


Chart 2.—Unsatisfactory results from one injection of protamine zinc insulin per day.

morning is within the normal range, the blood sugar levels during the day of administration are likely to be high. An example of such difficulties is illustrated in Chart 2. In these instances, although the blood sugar was mostly below 100 mg. per cent in the morning following injection of protamine, the blood sugars at noon and at 5:00 P.M. were high and these children had large quantities of sugar in the urine. Of fourteen children who are now receiving protamine zinc insulin and of approximately as many more who were on this or other protamine compounds during a seven-week camp period, only one is being maintained satisfactorily on a single daily injection of protamine without regular insulin. With one exception, however, all are receiving their entire insulin dosage at the time of the morning injection, the protamine being supplemented with a small amount of regular insulin in order to secure an adequate effect upon the noon and late

afternoon blood sugar. Even on this regime, it may be impossible to prevent the postprandial rise of the blood sugar after the evening

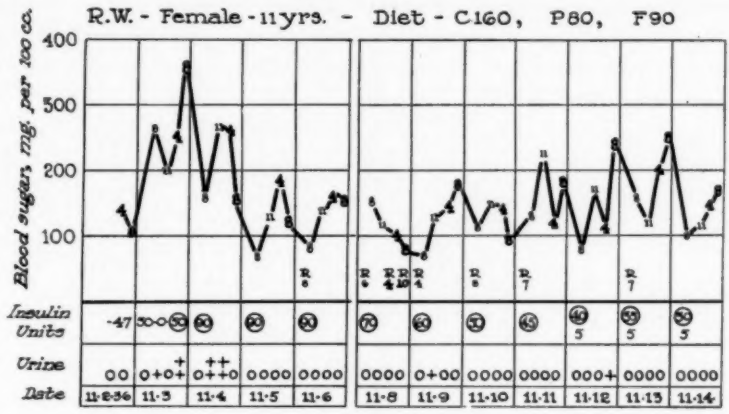


Chart 3.—Combined use of protamine zinc insulin and regular insulin.

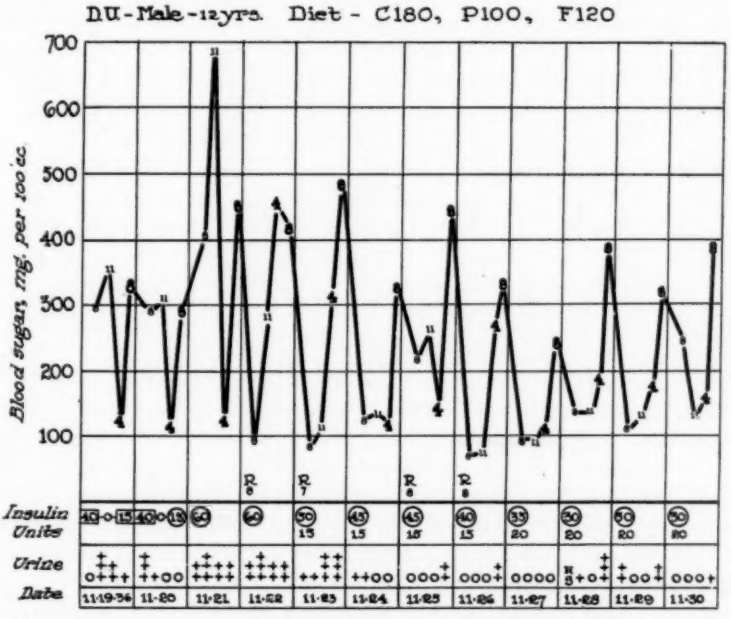


Chart 4.—Combined use of protamine zinc insulin and regular insulin. Note good glycemic balance except at 8:00 P.M.

meal. This is illustrated in Charts 3 and 4. In fact the blood sugar curve shown in Chart 4 is practically a mirror image of the blood sugar curves usually resulting from the administration of regular insulin in

two or three daily doses in that the 8:00 P.M. blood sugar is high in contrast to that at 8:00 A.M. This rise at 8:00 P.M. is frequently of such short duration that only small amounts of sugar appear in the urine. This does not appear to be important enough to necessitate the administration of an additional dose of regular insulin at 5:00 or 6:00 P.M.

An attempt was made to determine whether the administration of protamine insulin in single large doses at periods of the day other than at breakfast time would prove to be more efficacious. Several children were given their injections at 6:00 A.M., 4:00 A.M., 2:00 A.M. and 10:00 P.M. Chart 5 illustrates the effect upon the blood sugar after injection of protamine at the first three of these hours in contrast with several days when the injection of protamine was given before breakfast and supplemented with regular insulin. There were occasional days when the blood sugar was satisfactory after injections at all of these periods. Usually, however, in addition to the inconvenience of injecting the insulin at such hours, there was an actual disadvantage in regard to the blood sugar response. We have concluded that with the possible exception of 6:00 A.M. no added advantage is gained by such timing of the injections and that more satisfactory equilibrium is secured by a combination of protamine and regular insulin (in separate injections) at breakfast time. In a camp for diabetic children during July and August, 1936, we were able to secure somewhat more satisfactory blood sugar curves on single doses of protamine insulin without additional regular insulin than we have been able to maintain in the hospital or at home during the school months. It would appear, therefore, that the factor of activity may be important. If the daily activity is of sufficient amount and properly regulated, it may be possible to reduce materially the amount of regular insulin and possibly in some instances to eliminate it entirely.

One child is being maintained at the present time on a somewhat unorthodox plan. He is receiving 40 units of protamine insulin and 15 units of regular insulin in the morning and the same dosage again in the evening. With this regime he is in a much better state of stabilization than we have been able to maintain otherwise. This is simply evidence of the need of individualization in the treatment of diabetic children and an additional argument against too rigid establishment of rules.

It is generally stated that hypoglycemic reactions are less frequent and less severe when protamine insulin is employed as compared with the number and severity of these when regular insulin is employed. This appears to be the case particularly after the child is properly regulated. Nevertheless, reactions do occur, and they may be quite severe. Insulin shocks from protamine insulin are most likely to occur

from twelve to twenty-four hours after injection, so that if the insulin is given at breakfast time, the reaction may occur during the night hours. In our experience they have occurred most frequently in the early morning hours from 4:00 A.M. to 8:00 A.M. While it may be advantageous to prescribe a small amount of food at bedtime, our usual policy has been not to do this, but rather we have attempted to determine the amount of protamine necessary to maintain the blood sugar of the following morning at a reasonable level, and, when it is necessary to control the blood sugar at noon and at 4:00 P.M., to inject regular insulin at the time of injection of protamine. The onset of hypoglycemic reactions from protamine insulin may be slower and more insidious than after the injection of regular insulin. If these

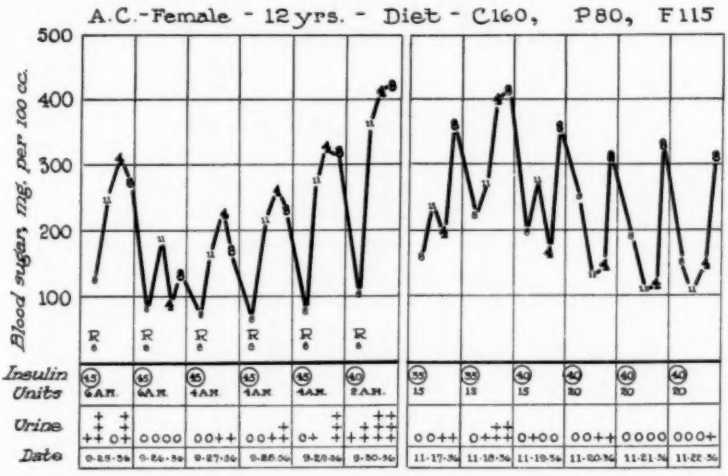


Chart 5.—Comparison of injections of protamine zinc insulin at 6:00 A.M., at 4:00 A.M. and at 2:00 A.M. with the combined use of protamine zinc insulin and regular insulin at breakfast time. Note high blood sugars at 8:00 P.M.

mild symptoms are disregarded, however, the child is liable to develop a very severe shock. Furthermore, because of the longer continued effect of protamine insulin, several shocks may result from a single injection (Chart 3). Thus, the child may have a second or even a third reaction after satisfactory treatment of the initial shock. It is important to instruct the child and his family about these facts.

Another slowly acting insulin preparation, crystalline insulin,* has been introduced recently. Several reports[5] concerning its clinical use have been published. In general, it is stated that this preparation has an effect upon the blood sugar which is less rapid and more prolonged than that of regular insulin but more rapid and less prolonged than

*Crystalline insulin was supplied through the courtesy of Frederick Stearns and Company, Detroit, Mich.

that of protamine insulin. It is said that its effect upon the blood sugar persists for from eight to fourteen hours. An attempt to use crystalline insulin in single large daily doses, as described for pro-

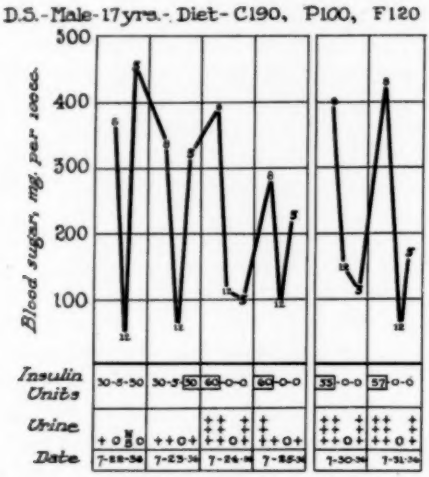


Chart 6.—Effect of one injection of crystalline insulin per day upon the blood sugar curve.

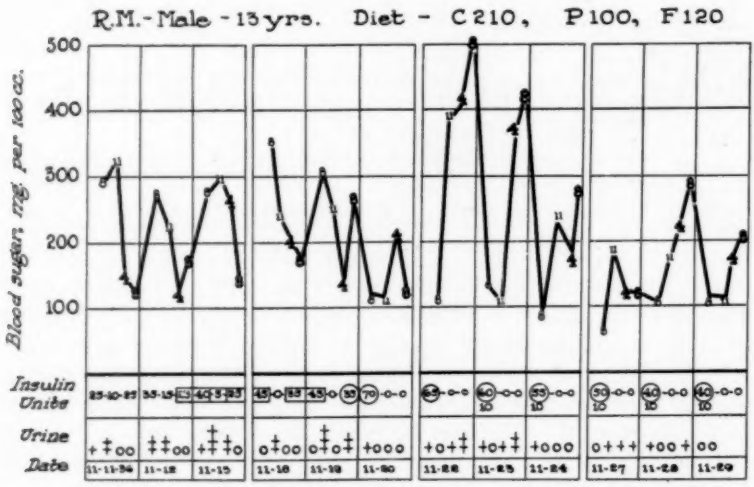


Chart 7.—Comparison of evening injections of regular, crystalline, and protamine zinc insulin.

tamine insulin, was unsuccessful in controlling the blood sugar for a period of twenty-four hours. This is illustrated in Chart 6. A comparison of the effect of evening injections of regular, crystalline, and

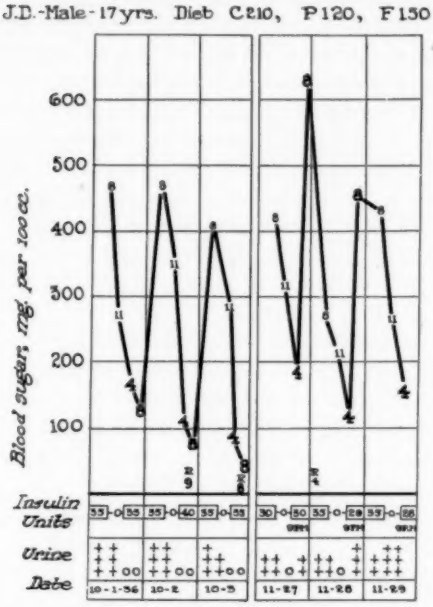


Chart 8.—Inadequate glycemic control with two injections of crystalline insulin per day.

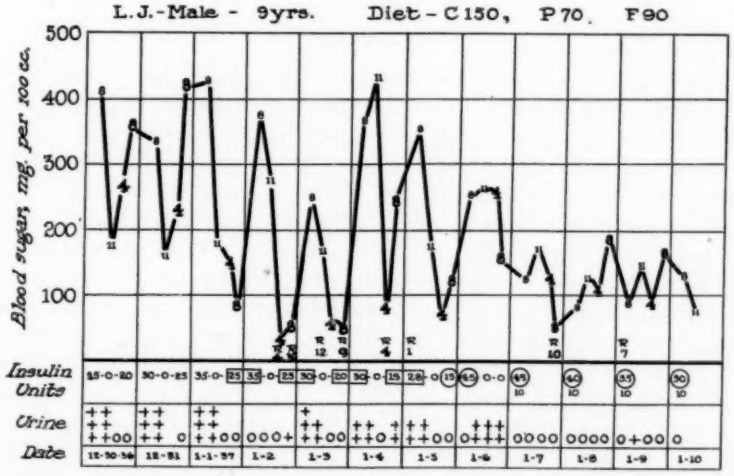


Chart 9.—Adequate glycemic control with the combined use of protamine zinc insulin and regular insulin administered at 8:00 A.M. in contrast to inadequate control on two injections per day of crystalline insulin.

protamine insulin upon the fasting sugar of the following morning is illustrated in Chart 7. There was no essential difference between the effect of regular and crystalline insulin in contrast to the good results obtained with protamine. Attempts were made in several children who were receiving two or three daily injections of regular insulin to control their blood sugar with two doses of crystalline insulin. An example of these results is shown in Chart 8. It was possible to control the blood sugars at 4:00 P.M. and at times at 8:00 P.M. by the morning injection. However, we have been unable to control the blood sugar during the night by injecting crystalline insulin either at 5:00 P.M. or 9:00 P.M. Practically all attempts to give a sufficient amount to lower satisfactorily the blood sugar of the following morning resulted in severe hypoglycemic reactions which occurred at some time during the night or early morning hours. Another comparison of results with regular, crystalline, and protamine insulin is demonstrated in Chart 9, in which much better results were secured with morning injections of protamine and regular insulin than with two daily injections of regular or crystalline insulin.

We have not used protamine or crystalline insulin in the treatment of diabetic coma and can see no reason for doing so. If children who are receiving protamine insulin develop an infection severe enough to lower their tolerance for carbohydrate, our policy has been to continue the protamine at essentially the same dosage and to administer, temporarily, regular insulin two or three times daily in amounts sufficient to control the glycosuria.

## SUMMARY

Our experience in the clinical use of protamine insulin has been distinctly satisfactory. The introduction of protamine by Hagedorn is probably the most significant contribution in the treatment of diabetes mellitus since the discovery of insulin. More recently the product has been improved by the addition of zinc and by the development of a compound which is stable for at least six months after mixing. This permits the marketing of protamine zinc insulin in an already mixed state. The method of administration by a single daily dose, suggested by Wilder and his associates, has aided materially in increasing the efficiency of the use of this product. In our experience, however, it has been the exception rather than the rule that diabetic children can be maintained in glycemic equilibrium without supplementary regular insulin administered at the same time as the injection of protamine. This is not a serious objection since the child continues to receive all of his insulin at one time, although in two different sites instead of at three or four times of the day. We feel that there is an advantage in making the initial injection of protamine in the evening, so that the blood sugar of the following morning is within the normal range.

We have not been able to determine that injection at other times of the day, with the possible exception of 6:00 A.M., has any advantage over the administration just preceding breakfast time. There is still need for clinical investigation regarding the time of administration and certainly a need for individualization in the treatment of each child.

In our experience the clinical use of crystalline insulin does not have sufficient advantage over that of regular insulin to warrant its general use at the present time, although it is worthy of further clinical trial.

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# THE NATURAL HISTORY OF RHEUMATIC FEVER IN THE FIRST THREE DECADES

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RHEUMATIC fever is a disease of long duration, having its usual onset and characteristic manifestations during childhood. At the present time it must be conceded that its etiology is unknown. Therapy is dependent mainly on current views as to its cause. The evaluation of etiologic hypotheses, as well as the appraisal of the results of preventive and therapeutic measures, must, on final analysis, take into consideration their relation to and influence on the natural course of rheumatic disease. This is well illustrated in critical studies concerning the etiologic rôle of respiratory infections in rheumatic children,[1] the influence of tonsillectomy,[2] vaccine therapy,[3, 4] drugs, and convalescent care on the incidence of occurrence and recurrence of rheumatic episodes.

What is the fate of the rheumatic child? What is the usual span of life? Is the heart always involved? Does the type of rheumatic manifestation have any prognostic significance? The answer to these, as well as to many other questions, may be ascertained from an analysis of the entire course of the disease in a representative series of rheumatic individuals. To chart the course of a chronic disease such as rheumatic fever, it is obviously necessary to follow it from its onset, throughout its course and to its end, a study which must take many years for completion. In a previous report, data based on a ten-year period of observation of the natural history of rheumatic fever,[5] covering the age range from childhood to adolescence, was presented. Another ten years have elapsed, offering an opportunity of presenting further data on the natural history of rheumatic disease in the first three decades.

This report is limited to a consideration of the course of the disease in 337 rheumatic subjects, 225 of whom have lived to their present ages of sixteen to thirty years, and 112 of whom have died of the disease during the twenty-year period of observation.*

In Chart 1 there is presented a graphic description of the clinical course exhibited by twenty living representative rheumatic individuals

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

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*This is a preliminary report of an analysis of the records of 1,000 children observed in a Cardiac Clinic from 1916 to 1936. The complete studies, to be published, are being made in collaboration with the Research Committee of the New York Heart Association.

from the onset of the disease to the year of last examination, a period of observation covering the first three decades. It may here be seen that the course of the disease from its onset in childhood is characterized by protean manifestations of activity and by a varied number of years (from one to seven) of freedom from recurrence or continuous years of manifestations of active infection. It is of importance to note the apparent freedom from symptoms of rheumatic activity after puberty at about the age of sixteen years. In a disease such as rheumatic fever

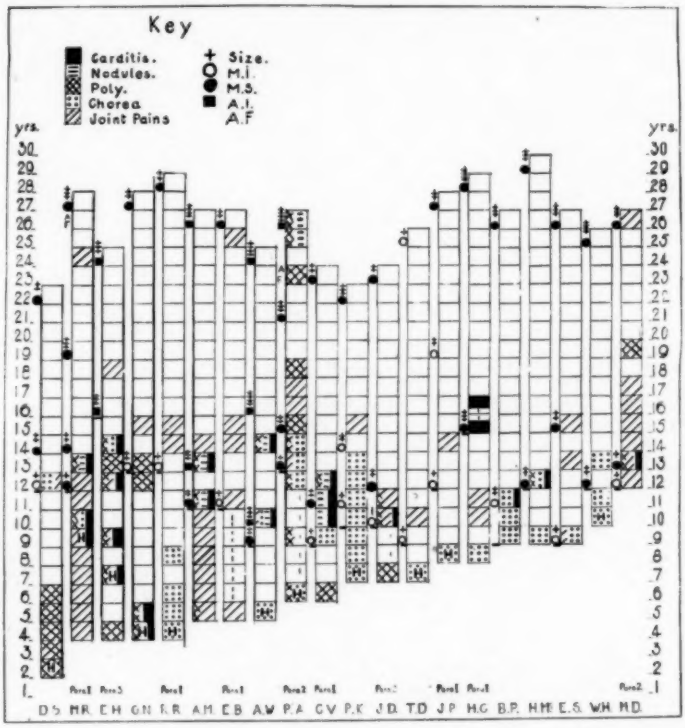


Chart 1.—The clinical course in the first three decades of twenty living rheumatic subjects illustrating the age of onset, years free from manifestations of active infection, and years of recurrences, as well as the anatomic diagnosis on last examination.

*H*, heart involvement first known; —, first observed.

it is hazardous to evaluate the rôle of any therapeutic measure. It is apparent, however, from a review of the literature that many investigators, following comparatively short periods of observation on small series of rheumatic subjects, have erroneously attributed a few years of freedom from recurrence to the therapy employed.

A comparison of the incidence of recurrences of rheumatic manifestations before and after the age of sixteen years in the living group is

presented in Chart 2. Here it may be seen that 13 per cent were free from recurrences before the age of sixteen years and 66 per cent after the sixteenth year. The recognition of the importance of the age factor in this disease is evident, particularly in view of the recent trend ad-

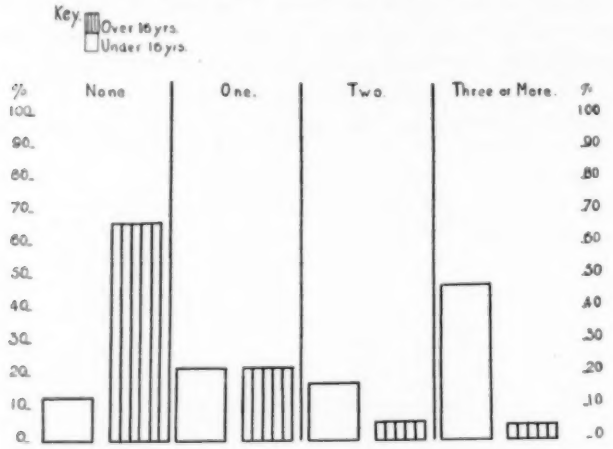


Chart 2.—Comparison between the incidence of rheumatic recurrences before and after sixteen years of age in 190 living rheumatic subjects.

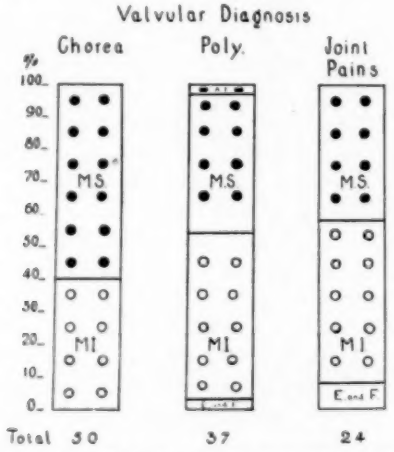


Chart 3.—Incidence of valvular lesions in rheumatic subjects (without active carditis) exhibiting chorea, polyarthritis, or joint pains. *E.* and *F.*, possible potential heart disease.

vocating the necessity of a change of climate for rheumatic subjects. Certainly from these observations it would seem necessary for rheumatic individuals to remain in such climates not a season or a year, but for the entire childhood, from the onset of the disease until after puberty,

before it can be said with any assurance that climate is an environmental factor of importance in this disease. It is of interest that the majority of these individuals remained in the same environment throughout the period of observation. A certain number of the children were in convalescent homes in the suburbs of New York City for periods of two months to two years. While these sojourns were beneficial and apparently influenced a speedy convalescence, the subsequent course of the disease did not appear to be significantly modified.

That the course of the disease in these twenty subjects, presented in Chart 1, is representative and characteristic of the entire group is evi-

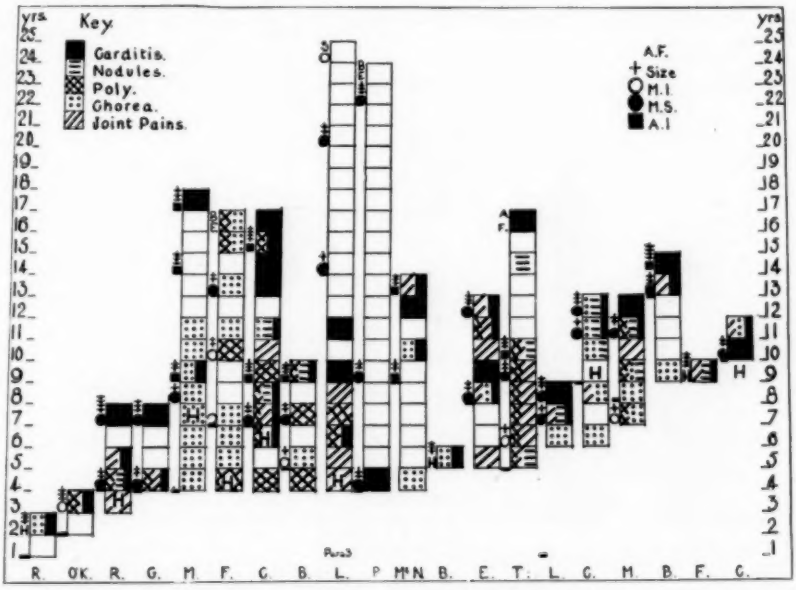


Chart 4.—Clinical course of twenty rheumatic subjects from the onset of the disease to death. *SO*, surgical operation; *BE*, subacute bacterial endocarditis; *AF*, auricular fibrillation.

dent from a further analysis of the data. All of the subjects but one, irrespective of the age of onset or the type of rheumatic manifestation (joint pains, polyarthritis, chorea, nodules, or active carditis), revealed evidence of cardiac involvement. The type of rheumatic manifestation, exclusive of active carditis, did not appear to be of prognostic significance. This is illustrated in Chart 3, where it may be seen that the percentage incidence of the various valvular lesions was comparable for the series of subjects presenting chorea or polyarthritis, with or without joint pains or joint pains alone. The presence of cardiovalvular disease in 98 per cent of these subjects indicates that an active

carditis which was subclinical, insidious and not recognized, must have occurred some time during the period of observation.

A comparison of the course of the disease, for the living and for the deceased groups, from the onset to the end of the period of observation or death, indicates that the disease is self-limited. In Chart 4 are presented graphically the rheumatic manifestations exhibited by twenty representative individuals from onset to death. Here it may be seen that, with the exception of the increased incidence of active carditis, the course of the disease during childhood in the living and deceased groups is similar. In the total group the majority of the deaths followed a

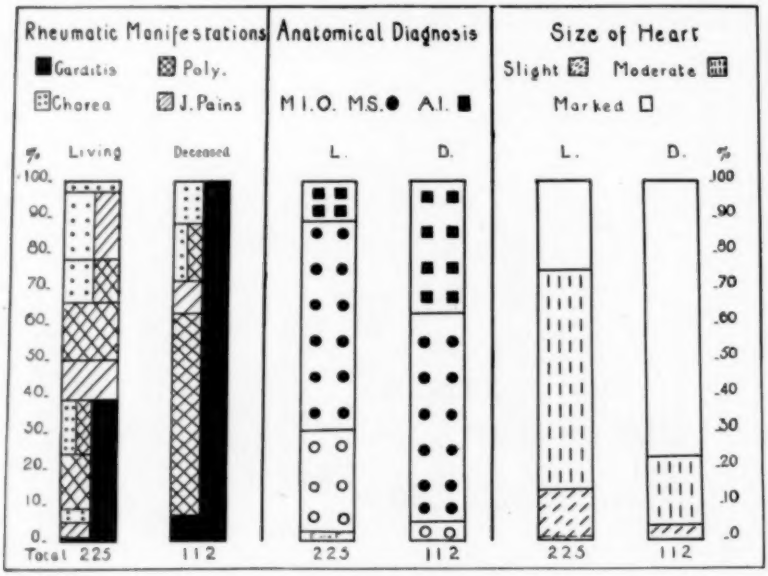


Chart 5.—A comparison of the rheumatic manifestations and anatomic diagnoses in 225 living and 112 deceased subjects.

terminal active carditis. About 85 per cent succumbed before the age of seventeen years, the average age at death was 12.6 years, and the age range at which the greatest number of deaths occurred was from twelve to sixteen years, inclusive. Only deaths due to the disease are included in the series. There were three deaths due to subacute bacterial endocarditis, and one following cesarean section and sterilization in a para iii.

A comparison of the rheumatic manifestations, the valvular diagnosis, and the size of the heart in 225 living and in the 112 deceased subjects presented graphically in Chart 5 is of interest. The disease was of greater severity in the deceased group as judged by the incidence of active carditis, multiple valvular lesions, and greater cardiac enlargement. The low incidence (39 per cent) of active carditis in the living

group should be noted. In the majority of the children (61 per cent) the cardiac involvement progressed insidiously with probable minimal myocardial damage, giving rise to symptoms which were subclinical and not recognizable. When the symptoms were of sufficient degree to be diagnosed, the cardiac damage was greater and the mortality higher. Of a total of 87 living subjects experiencing symptoms of active carditis, 48 per cent had marked cardiac enlargement and 91 per cent had multiple valvular lesions, compared with 27 per cent and 56 per cent, respectively, for 138 subjects in whom the presence of an active carditis was not recognized during the course of the disease. In this latter series many presented regression of characteristic physical signs of cardiovalvular disease with persistent enlargement of the heart.[6] The relation

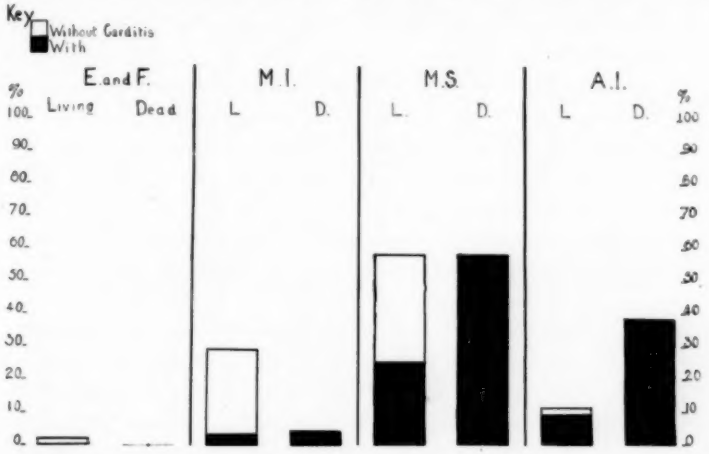


Chart 6.—Incidence of the type of valvular lesions as related to the occurrence of active carditis in the 225 living and in the 101 deceased subjects. *E. and F.*, possible potential heart disease.

between the occurrence of active carditis and the degree of cardiac involvement is illustrated in Charts 6 and 7.

While one cannot, with assurance, give any prognostic prediction in an individual subject, the probability is that from the standpoint of morbidity and mortality a child who does not present recognizable symptoms of an active carditis may be expected to exhibit lesser degrees of cardiac involvement in terms of cardiac size and multiple lesions and to have a longer span of life. From analysis of the data secured, it is evident that the heart is practically always involved to some degree in rheumatic disease. The mildness of symptoms, the difficulty of recognizing the presence of an active carditis, and the regression of characteristic physical signs have led some observers to the conclusion that a certain percentage of rheumatic individuals do not present evidence of cardiac involvement.

Undue emphasis, however, has been placed on the anatomic findings and not sufficient on the ability of the heart to carry on its work. It is, therefore, of interest to consider to what degree these 225 rheumatic individuals were incapacitated due to cardiac symptoms during the observed course of the disease in the first three decades.

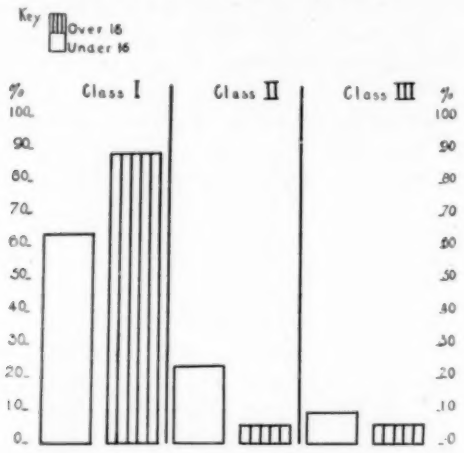


Chart 7.—Incidence of the degree of cardiac enlargement as related to the occurrence of active carditis in the 225 living and in the 111 deceased subjects.

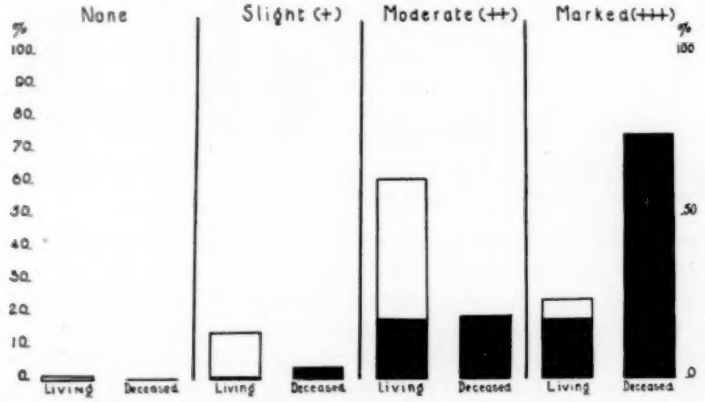


Chart 8.—Comparison of functional classification in 225 living subjects during the years before and after the age of sixteen years.

Class I, subjects able to carry on normal activity without cardiac symptoms.
Class II, ordinary activity followed by cardiac symptoms.
Class III, cardiac symptoms (dyspnea, etc.) at rest.

All of these subjects were permitted, when free from symptoms of an active infection, to carry on their normal activities, exclusive of competitive athletics. A comparative analysis of the functional classification recorded for these 225 rheumatic subjects during the period of observa-

tion for the years before and after the age of sixteen is presented in Chart 8. Here it may be seen that 64 per cent of the children for the years to the sixteenth year and 88 per cent for the years after this age were able to carry on their ordinary work and play without circulatory symptoms (Class I). It must be borne in mind that all of these subjects presented evidence of rheumatic heart disease. For the 39 per cent who presented symptoms of active carditis (classification recorded was Class II and Class III), the circulatory symptoms were present on slight exertion or were present at rest. Obviously, these patients were not permitted any exercise.

These observations would seem to indicate that a diminished exercise tolerance is more closely related to the presence of an active carditis than to the resulting valvular damage or cardiac enlargement. That this is probable is also indicated by the normal exercise tolerance of the majority of these subjects with rheumatic heart disease who have lived and reached the ages of sixteen to thirty years.

The subsequent clinical course to be experienced by these individuals in the fourth and fifth decades must await a further period of continued observation. It is permissible, however, to speculate concerning the probability that the course of the disease in these subjects may be more favorable than is indicated from the valuable study, "The Course of Rheumatic Heart Disease in Adults," reported by De Graff and Lingg.[7] Their observations were made in an adult cardiac clinic where it might be expected that only individuals suffering from symptoms would report for treatment. In our series of observations only 34 per cent over the age of sixteen who suffered rheumatic recurrences and 12 per cent who experienced circulatory symptoms might be expected to report to a clinic for treatment. It was only after very intensive follow-up that it was possible to secure the attendance of our patients after the age of sixteen. The majority, who were free from symptoms, could see no need of medical supervision.

## SUMMARY

An analysis of the clinical course exhibited by 225 rheumatic subjects who have lived to their present ages of sixteen to thirty years, and 112 individuals who have succumbed to the disease during a twenty-year period of observation, has been presented. The onset of the disease from childhood is characterized by protean manifestations of activity and by a varied number of years of freedom from recurrence or continuous years of manifestations of active infection. After puberty, about the age of sixteen years, the majority of the subjects (66 per cent) were free from recurrence of symptoms, compared with 13 per cent before this age period. The practical importance of consideration of the age factor in this disease has been discussed.

From a comparison of the course of the disease in the living and in the deceased series of subjects, it appears that the disease is self-limited, death being due in most instances to fatal active carditis. While the first attack of carditis may be severe and fatal, the majority of the deceased subjects survived subsequent recurrent active carditis. The average age of death was 12.6 years, and the greatest incidence was in the age group of twelve to sixteen years, inclusive, for the series.

The care and management of these patients during the period of observation is not within the scope of this report. It is, however, of some interest to note that the children who experienced several intercurrent years of freedom from manifestations of rheumatic activity, remained in the same environment. Those who succumbed to the disease and those who survived with minimal degree of cardiac damage received comparable medical supervision. It is difficult to reconcile some current etiologic hypotheses with the observed course of the disease in these subjects.

The type of rheumatic manifestation, exclusive of active carditis, did not appear to be of prognostic significance. The incidence of heart disease was comparable whether patients exhibited joint pains alone or chorea or polyarthritis with or without joint pains. All of the subjects presented evidence of cardiac involvement, although in only 39 per cent were the symptoms of carditis above the clinical horizon and capable of recognition. When the symptoms of active carditis were of sufficient degree to be diagnosed, the subsequent amount of cardiac damage, that is the multiple valvular lesions and marked cardiac enlargement, was greater and the mortality higher. During the course of the disease physical signs of valvular involvement may disappear, may be inconstant or uncharacteristic, leading to the erroneous opinion that the heart is left unscathed. The presence of considerable cardiac enlargement, established by adequate roentgenologic examination in a large series of these children who were under continuous careful observation, indicates the limitations of a diagnosis of the absence of cardiac involvement in rheumatic individuals based on physical examination alone.

It is of some prognostic importance to note that the majority of these rheumatic individuals who survived were able to carry on their work and play without circulatory symptoms, particularly after puberty. The future course of the disease in these individuals must await a further period of continued observation for final comment. It would seem likely, however, that the usual unfavorable prognostic opinion that the majority succumb during the third and fourth decades is influenced by observations which are limited to adult patients who are under observation because of symptoms or by postmortem statistics. There may well be in the general population a considerable number of rheumatic individuals in whom the disease has been mild or unrecognized and the pres-

ence of heart disease unknown. Our own observations, as well as the frequent accidental discovery of mitral stenosis during routine physical examination or postmortem examination, favor this view.

Accumulation of adequate data as to the true incidence, morbidity, and mortality of this disease is a vital need. Such information can only be collated from studies of representative series of subjects under continuous observation from the onset of the disease throughout its course to its end.

An adequate comprehension of the natural history of rheumatic fever is the only reliable criterion available at the present time for considering critically current etiologic hypotheses and for evaluating various therapeutic measures.

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# BODY TEMPERATURE VARIATIONS IN APPARENTLY HEALTHY CHILDREN

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VARIATIONS from the accepted normal body temperature, especially in childhood, have always given rise to much anxiety. The red line upon the clinical thermometer, now an almost universal household appliance, has so fixed itself in the mind of the parent, nurse, and even family physician that, despite the mass of clinical evidence that these variations are compatible with health, there still appears to be much uncertainty as to what should be considered a fever of obscure origin.

In order to do something that might be of help in alleviating unnecessary worry, more than 750 apparently healthy children of various age groups were studied with a view to determining the frequency of readings above the accepted normal, the variations that might be expected at intervals during the day, and the effect upon the temperature of environmental changes and nervous excitement.

Evidently the temperature of the monkey is more susceptible to outside influences than that of man, but, if we are willing to accept the monkey as fairly close to the human, we find in him some very real evidence that the excitement of everyday life, both physical and mental, may cause real variation.

Many years ago Simpson and Galbrath, in Edinburgh, and C. Y. White and Herbert Fox, at the Philadelphia Zoological Gardens, were able to show surprising diurnal variations in tuberculin-negative monkeys, which had hitherto not been appreciated. The findings were probably, as the former suggest, due to the fact that no one had previously taken the temperature of the healthy monkey at three o'clock in the morning. Dr. Fox found that the daily temperature of the monkey per rectum at 3 P.M. is generally between 101° and 102° F. Starting at the high point, 3 P.M., the temperature gradually declined and the low point was reached at about 3 A.M., after which a gradual rise occurred following in reverse order the same course as the fall during the preceding twelve hours and again reaching the high point at 3 o'clock in the afternoon. The average of this fall in the monkeys was 3.5° F. although he found in a healthy monkey a fall as great as 7° F. Simpson and Galbrath, studying the effect of various forms of excitement, found that the temperature was increased in direct proportion to the degree of excitement. That children are similarly affected we

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have tried to show, with some success, working with a group at the Schenectady Children's Home.

A composite chart published by Dr. Fox in "Diseases of Captive Wild Mammals and Birds" representing the average rectal readings of 18 nontuberculous monkeys taken at four-hour intervals over a period of forty-eight hours showed the high points at 103° and 102.8° F. and the low points slightly above 99° F. We were able practically to reproduce this picture with 18 apparently healthy children, the only difference being that instead of a definitely single high point at 3 P.M. the temperature practically reached its height at 11 A.M., and there was little variation in the curve between 11 A.M. and 7 P.M. The fall from the high to the low point was as surprising in the children as it was in the monkeys, possibly, also, because the temperature of a healthy child had not previously been taken in the early hours of the morning.

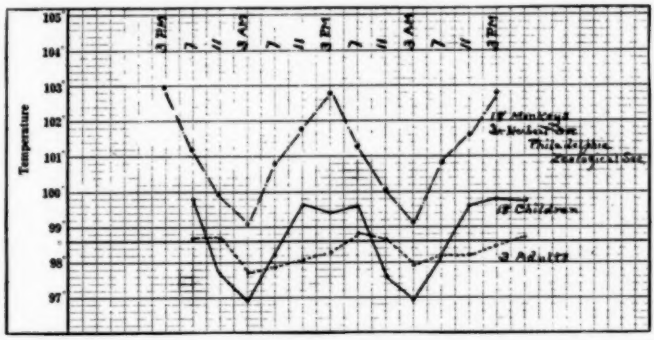


Fig. 1.—Comparative charts of the temperature variations of monkeys, children, and adults. The chart for monkeys is reproduced with the permission of Dr. Herbert Fox and the Philadelphia Zoological Society.

Records of three adults, taken under similar conditions, show comparatively trivial periodic variations. The temperature-regulating mechanism of the unstable child is evidently less, though little less, susceptible to environmental changes than is that of the more unstable monkey. From this single observation it would appear that ordinary environment has little effect upon the body temperature of the adult but that it has a very definite effect upon the young, and there is further evidence that this is true. With his permission, I am reproducing, in comparison with our own, the chart prepared by Dr. Fox who has found that the younger the child, the deeper is the variation in the curve (Fig. 1).

Another experiment performed upon the monkey by Simpson and Galbrath, and which we were able to repeat with our children, would seem very conclusive evidence of the influence of environmental changes. To make possible the observation our two seven-year-old boys had to be hospitalized but, since they were institution children, this

factor probably had little effect upon the result. Like the monkey they were kept awake during the night, fed and treated as in the day, and put to sleep in a darkened room after a "supper" in the morning

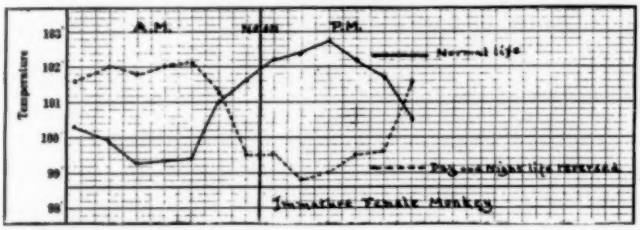


Fig. 2.—Effect of reversal of day and night life upon the temperature curves in the monkey. (From Simpson and Galbrath, Trans. Royal Soc. of Edinburgh, 1905-1907.)

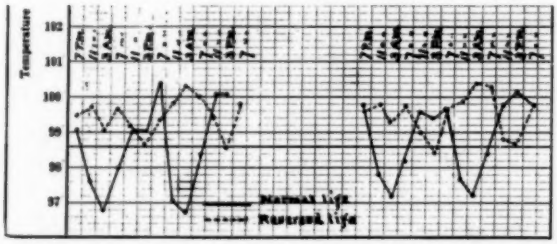


Fig. 3.—Effect of reversal of the day and night life upon the temperature curve in children.
At left: a single child with his own normal.
At right: a composite of 2 children and 18 normal children.

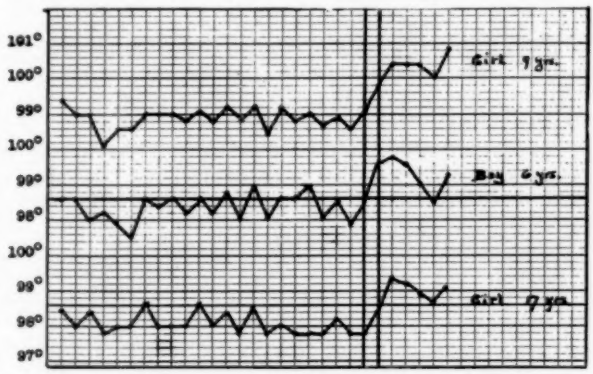


Fig. 4.—Effect of mental excitement upon the temperature curves of three children.

to be roused for "breakfast" in the late afternoon. Their temperatures were taken, by rectum, at four-hour intervals as in the previous experiment and the usual curves of day and night were found to be reversed—not so markedly as that of the immature female monkey but very definitely, nevertheless.

The chart showing the results of the experiment on monkeys is reproduced as Fig. 2; the chart of one of the children plotted against his normal and a composite chart of the two boys against a composite of the 18 normal children, as Fig. 3.

Intensive physical exercise has been known to cause marked rise in body heat. We have been told of a runner whose temperature rose to 104° F. after a race, and it has long been accepted as a clinical fact that nervous and mental strain can cause a similar though probably not so great an elevation.

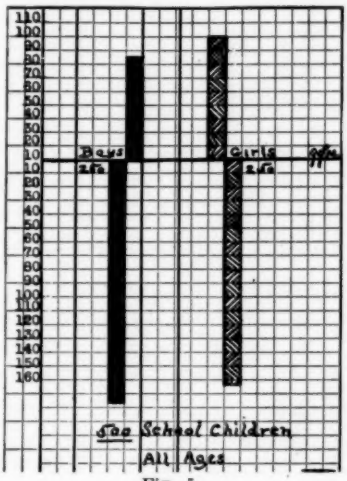


Fig. 5.

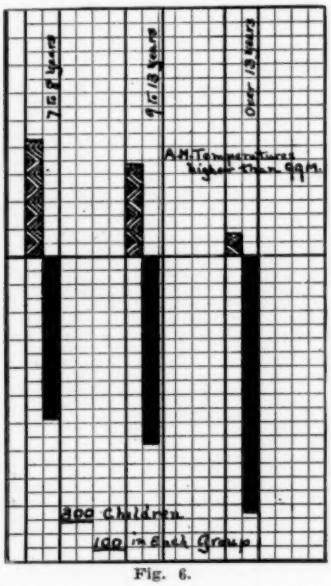


Fig. 6.

Fig. 5.—Showing frequency of high oral temperatures in apparently healthy children.

Fig. 6.—Showing the higher temperatures in the younger age groups.

In order to confirm this influence of mental excitement experimentally and to divorce it from the physical, the temperatures of more than forty children were taken night and morning over a period of four weeks in order to establish their normal temperatures, and at the end of the period they were subjected to exciting experiences. In a fair proportion, though by no means in all, the thermometers registered an elevation during the period of excitement. The observations were recorded simultaneously with a thermometer for each child; they were, however, not always made with the same instrument before and after, so that criticism of technic might be offered. However, the error should be but slight. Three of these charts are shown in Fig. 4.

During the past school term, through the courtesy of Dr. J. E. Burke, in charge of medical inspection in the public schools of Schenectady, we were able to secure temperature readings of 717 children of various age groups. The readings were taken at approximately the same time by seventeen nurses in more than twenty schools, a group of about thirty in each school and about equally divided as to sex. The temperatures were taken during the early part of the morning session when they would naturally be at a comparatively low point for the day.

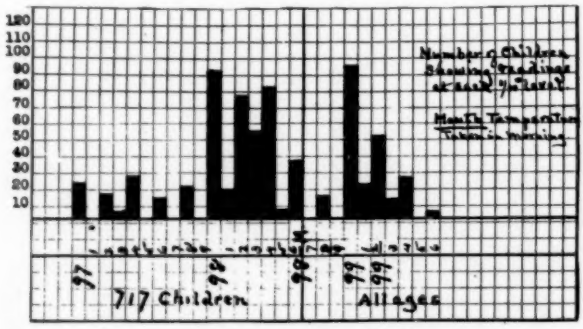


Fig. 7.—Designed to show the normal temperature range compatible with health.

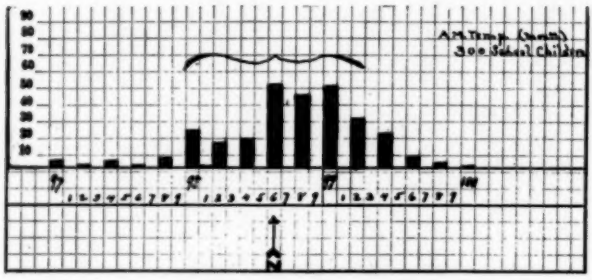

Fig. 8.—Confirming the findings of Fig. 7.

The group was studied with three objects in view: to determine how many apparently healthy children during their ordinary daily routine showed a temperature definitely higher than the accepted normal of 98.6° F. (oral); to determine the influence of age upon this upward deviation from the accepted normal; and to obtain some data which might be of help in defining the limits compatible with health.

To answer the first question a chart was plotted with a base line of 99° F. (oral). Five hundred children were represented, equally divided between boys and girls, and of these 157 (31.4 per cent) were found to have registered above 99° F. by mouth. The girls ranged

slightly higher than the boys, showing 35.6 per cent above the 99° F. line as compared with 29.2 per cent (Fig. 5).

To determine the possible influence of age upon the height of the temperature in the supposedly healthy child, the simultaneous morning mouth readings of 300 children, busy with their regular school work, were divided into three age groups of 100 each, and a chart similar to the previous one was made to show the number of children whose temperatures ranged above the arbitrary 99° F. line. The results were as follows (Fig. 6):

In the seven-to-eight-year group the percentage was 43. That is to say that nearly half, or 43 per cent, had temperatures definitely above the accepted normal.

In the nine-to-thirteen-year group one-third, or 33 per cent, reached these higher levels, whereas in the group representing children above the age of thirteen years only 8 per cent showed readings of 99° F. or above. This picture appears to show, very clearly, that the older the child, the more stable is the heat-regulating mechanism.

In order to obtain data which might be of help in defining the limits compatible with health, a graph was prepared to show the number of children whose readings reached each temperature level. It would seem justifiable to consider as the normal range that in which the great proportion of the temperatures fell.

Figure 7, comprising the morning oral readings of 717 children, shows this normal range between 98° and 99.2° F. but may be subject to slight error because of the fact that some of the readings were recorded in tenths and some in fifths of a degree. Since they were all charted in tenths, correction of the error would throw a larger number into the higher brackets and further confirm our premise. Unfortunately correction could not be made because of loss of some of the data.

Figure 8, which comprised 300 of the corrected figures, is little different, in favor of the higher readings.

We feel that we have been able, to some extent, to confirm the clinical belief that slight elevations of temperature are compatible with health and that there is justification in assuming that an oral reading slightly above 99° F. and a rectal reading slightly over 100° F. need not, *in the absence of other findings*, be considered evidence of disease.

We wish to express our appreciation of the help given us by Dr. John E. Burke, director of health of the Schenectady public schools, without whose cooperation this investigation would have been impossible.

# NEWER ASPECTS OF THE WHOOPING COUGH PROBLEM

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IT IS said that patients suffering from whooping cough pass through incubation, catarrhal, paroxysmal, and convalescent stages. Those who treat many cases of this disease soon realize that the paroxysmal stage should be subdivided into an early paroxysmal stage with a staccato-like cough and a later paroxysmal stage in which there is a staccato-like cough ending with a whoop and often accompanied by vomiting. The various stages of the disease overlap too much to be arbitrary as to the limits of each period, but usually there seems to be sufficient time elapsing between the onset of the paroxysms and the beginning of the whoop to be of some clinical significance, especially when the effects of therapeutic procedures are to be measured. One might then divide the stages of the disease into incubation, catarrhal, paroxysmal, paroxysmal and whooping, and convalescent stages.

Leslie and Gardner[1] have described whooping cough bacillus as having four phases of existence (phases I, II, III, and IV). They base their conclusion upon evidence obtained from agglutination tests. If, however, an agglutinin titer reaction value is to be taken as evidence of the existence of a phase of an organism, then the ultimate phase would be that in which the serum has the highest response as represented by serum titer values. Theoretically, if this titer value is 1:25,000 then the other end of the life cycle phase of any organism is one in which the serum agglutinin value approaches zero. Theoretically, and from a mathematical standpoint alone, their conclusions could not be valid since in this instance, at least, there should be 25,000 or more phase possibilities. The author and his associates[2] repeated the work of Leslie and Gardner[1] and have shown that it would be difficult and well-nigh impossible to limit the life cycle of these organisms to four phases as they have done, although it is probably true that an organism during its period of existence passes from one phase of growth to another. It would seem more logical when referring to *H. pertussis* to speak of the "disease-producing" and the "avirulent," or "fixed," state of its existence.

The incubation and catarrhal stages of whooping cough last anywhere from eight to fourteen days. During this period and for a short time thereafter extending into the paroxysmal stage, phase I or disease-producing organisms are easily isolated. It is during this stage that the

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disease is probably most contagious. As high as 80 per cent of plate cultures have been positive in the earlier periods of the paroxysmal stage. Paradoxically enough when the child is well into the paroxysmal and over into the paroxysmal and whooping stage, when he actually has become sickest from the disease, it begins to get relatively more difficult to find these phase I organisms. The disease becomes less contagious and easier to control even though the patient may actually be clinically worse. On the other hand, as the whoop becomes more pronounced and the disease progresses, it becomes easy to recover the sticky mucoid ball of exudate that is coughed up with each whooping spell. It is not the freshly isolated phase I bacillus which causes the whooping cough of this disease, but this material, possibly an exudate, which when stained appears to be composed of *Mucor mycelium*.[3] This sticky material produced during the growth of the bacillus is the thing that causes the whooping cough. This material is not found in the human being during the catarrhal stage of the disease, and it is highly significant that phase I organisms, or the disease-producing phase I organisms obtained early in the disease, do not produce this sticky material no matter how long they are grown on blood agar and no matter what species of blood is used—horse, sheep, or human. One need but review the history of any case of whooping cough to recognize the importance of these observations. The child in the incubation period is not ill; he merely has acute rhinitis. This is at a time when phase I organisms are found most easily. The child gradually gets worse and paradoxically the chances of isolating the disease-producing phase of the organism's existence decreases. Phase I organisms, at the disease-producing stage of the organism's existence, initiate the disease, but they do not produce the material that causes the troublesome cough which gives the disease its name and its most common characteristic. In short, only after the organism becomes acclimated to the host is the organism able to produce the exudate in amounts sufficient to cause the whoop. The human disease-producing phase I type of organisms becomes acclimated and soon changes to the "fixed" or "resistant" state of the organism's existence, and this latter phase type thrives and grows on nearly any experimental medium. I have been able to produce the same sticky pertussis mucoid material in vitro, the same sticky material in all physical characteristics as that mucoid material coughed up by children after a whooping spell.[4]

Other higher bacillary forms, as for example, the colon bacilli, when grown on unfavorable mediums rapidly mutate into the avirulent coccoid forms of old age, and the organisms soon die if kept on the same medium.[5] Bacillary forms are virulent forms of the ordinary type of bacillus. When *H. pertussis* bacillus is first isolated from the human being, it appears in a coccoid state. Curiously enough this seems to be the most virulent form for human beings. It produces the highest

agglutinin titer in the serums of rabbits which have been injected with it,[2] kills them most quickly,[6] and from an immunologic standpoint acts totally unlike other coccoid forms of bacilli. This coccoid form of *H. pertussis* becomes bacillary with frequent transplantations and acclimation to any medium. Once it assumes the bacillary form, it becomes so resistant that it grows and keeps its shape on nearly any medium.[7] This is in decided contrast to ordinary bacillary forms which become coccoid with repeated transplantations under unfavorable circumstances. One can keep *H. pertussis* in the coccoid form only by providing blood for its multiplication. In other words, blood influences the growth of the organism unfavorably and keeps it in its coccoid state. One might gain the impression from reading the literature that the coccoid type is the type species since it initiates the disease in man. This could not be so, for on general principles such a belief would violate the fundamental concept that that type of species is probably the true, pure and dominant strain which can live under any circumstances. Since all coccoid pertussis types are eventually reduced to a bacillary unit if they live, it would seem logical to believe that the so-called fixed bacillary form, the form ignored by most workers in the disease, is the type species itself and that the coccoid form or the human disease-producing phase has been made thus by some unfavorable circumstance of medium environment. Thus the coccoid form would merely represent a more resistant stage of temporary existence—resistant because of the growth environment. This belief does not violate the standard conception that bacilli become coccoid under unfavorable circumstances. It would merely leave unanswered how *H. pertussis* becomes coccoid in the human being and why this form is necessary to initiate the disease.

The mucoid material produced by the fixed type of the pertussis bacillus is not the soluble toxin referred to by Mishulow and her coworkers.[8] It cannot be confused with Krueger's endoantigen[9] and certainly has nothing in common with the freshly isolated organism. It is a new substance first grown by the author and described by him and his associates,[4, 10] a product produced during the course of bacillary growth just as the toxin of diphtheria is produced during the course of diphtheria by the diphtheria organisms. The toxin of the latter causes diphtheria; the exudate of the fixed phase organism brings about the whooping cough stage. This material, of course, is not a toxin in the sense that diphtheria toxin is.

In a fluid type of culture medium the organisms grow rapidly on the bottom of the flask after the fourth or fifth day. By the ninth day, this growth has extended along the bottom and up the sides as a thick tenacious film. Clumps connected with the bottom of the flask by a thick, ropey string grow on the surface of the media. After fourteen days, the culture flask contains a thick, stringy, mucilaginous mass which adheres firmly to the smooth glass and is delivered only as large masses of semi-

gelatinous consistency. After centrifugation, the slightly cloudy supernatant fluid was passed through a Berkefeld N and W filter. The filtrate obtained was clear and contained the factor previously described which produces a reaction in human beings ill with the disease when injected intradermally, but only after the patient has had the infection for about seven to ten days.[10] This filtrate was injected into rabbits, and it was found to be specific, since agglutinins were formed for the phase pertussis organisms which had been used to inoculate the culture medium from which the filtrate had been obtained. The method and manner of injection were as described before.[2] Previously, I found that the specific factor in the filtrate (probably an exotoxin) was precipitated out at pH 4 with a weak solution of acetic acid. This procedure had to be repeated twice before all of this factor could be precipitated out. It was then found that the entire specific factor could be precipitated out in one step by using an excess of acetic acid. It has also been found that the precipitate goes back into solution when the pH of the solution has reached 7.2.

The material found in the original centrifugate not only contained organisms and the specific factor just mentioned, but a mucoid metabolic material as well. The problem now was to separate the organisms from this mucoid material. Further centrifugation did not cause complete separation of organisms from the centrifugate. However, it was found that the pertussis mucoid material could be taken up in physiologic saline by shaking the mixture of organisms and mucoid material in saline. This was done several times until the saline took up no more material and remained clear. After each shaking the whole was centrifuged, and the centrifugate combined. The supernatant fluids were also combined separately. The centrifugate remaining contained only organisms and could be discarded while the mucoid metabolic material in solution in the supernatant fluid could be precipitated out by an excess of acetic acid and the material could be standardized at any determined wet weight figure and resuspended in saline. At pH 7.2 there was a relatively stable suspension. The material, however, did not go into complete solution.

Krueger ground up the freshly isolated phase I organisms and used the endoantigen in treatment and prevention. Sauer and many others used only the freshly isolated organism itself. Neither Krueger's endoantigen nor Sauer's vaccine has modified the course of the disease in children admitted to our wards.[11] This is what one would expect if immunity against this disease could be considered as an immunity that would have to be established against the mucoid product of growth rather than an actual immunity against the freshly isolated bacteria themselves. Immunity against diphtheria toxin is not immunity against diphtheria organisms. Nor did diphtheria organism vaccine protect fully against diphtheria infection.[12] It is curious also in view of

Krueger's experiments with pertussis endoantigen that before toxin-antitoxin was used to prevent diphtheria, Hewlett[13] claimed that the endoantigen obtained from the ground cultures of *B. diphtheriae* organisms protected guinea pigs against as high as from 3 to 4 M.L.D.

That this thought on the mechanism of immunity in this disease may have some basis is seen from the following experiments: Serums obtained from rabbits, sheep, and horses injected with phase I organisms to the point where the agglutinin titers of the various blood serums

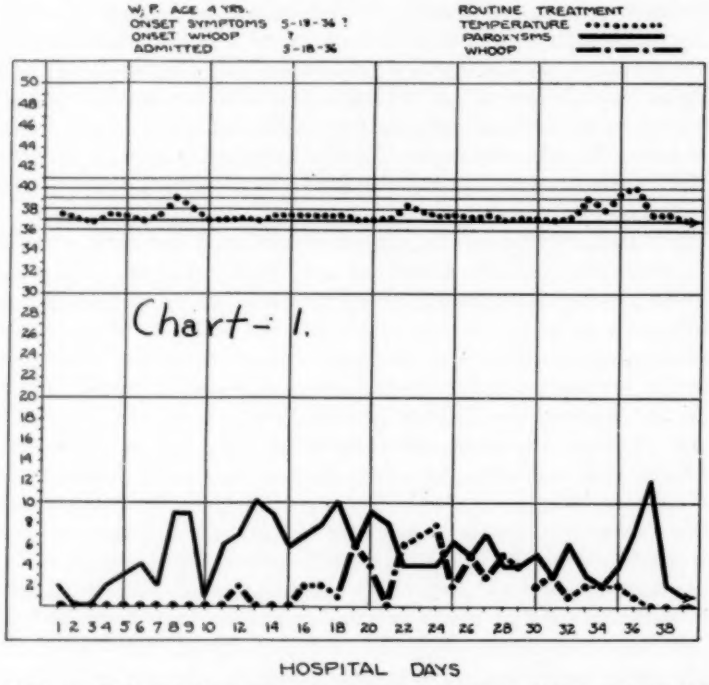


Chart 1.—W. P. and all of the patients whose charts are shown were not given any sedatives. This particular patient did not receive any specific factor. He was still whooping when discharged from the hospital forty days after the date symptoms were first noted. The child had a mild infection.

reached titers as high as 1:40,000 did not modify or prevent the clinical disease from occurring in human beings.[14] In fact, if anything, the clinical condition was usually made worse. When phase I organisms of a high titer, washed fresh organisms, or the endoantigen obtained from phase I organisms that had been ground in a ball mill were combined in each instance with serum of high titer and then injected intradermally into human beings ill with pertussis, there was an accentuation of the local reaction not present when any one of these materials was individually injected—an allergic type of response. Likewise, when

combinations of freshly isolated phase I organisms and serums of a high titer such as described were injected intraperitoneally into guinea pigs, the animals thus injected died as soon as the controls, and the pathologic reaction seen was more severe in the protected group.[14]

It has likewise always been a curiosity why, if freshly isolated organisms are the only ones against which an immunity must be built in this disease, it is so extremely difficult to demonstrate agglutinins of high titer for the organisms of phase I in the blood serums of children who

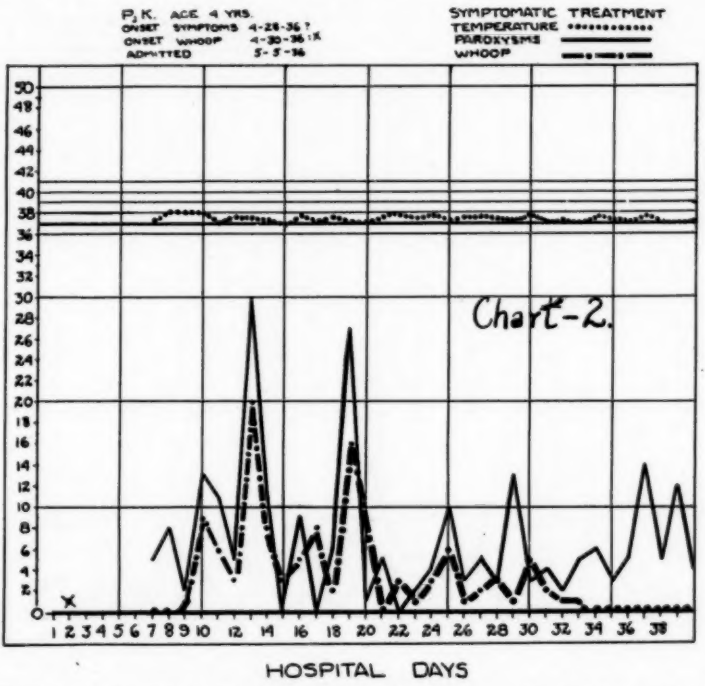


Chart 2.—P. K. This is the chart of a more typical case showing the number of whoops and the time of their occurrence. The child was still whooping and coughing at the time of discharge forty days later.

have recovered. It would seem more logical to believe that children improve as soon as they can dispose of the mucoid material produced during the metabolism of the organisms and that recovery occurs when this comes about, just as recovery occurs in diphtheria when enough antitoxin is manufactured. Reasoning analogously, it is probable that an artificial active and passive immunologic principle could be obtained by using this mucoid material as the antigen; however, the mechanism of immunity in the human being may be the combined result of a sensitization-desensitization phenomenon and an antigen-antibody reaction.

Since it is thought that a cure for the clinical disease is brought about when pertussis mucoid material is counteracted or disposed of, it is quite possible that actual attacks of the disease might be shortened by injections of this specific factor.

Before attempting to draw conclusions as to the efficacy of specific measures, normal untreated cases have to be studied. One needs care for only a few cases of this disease to begin to appreciate how variable and unpredictable is its course in the average individual. It does not take the experiences of many cases to convince us of the utter futility

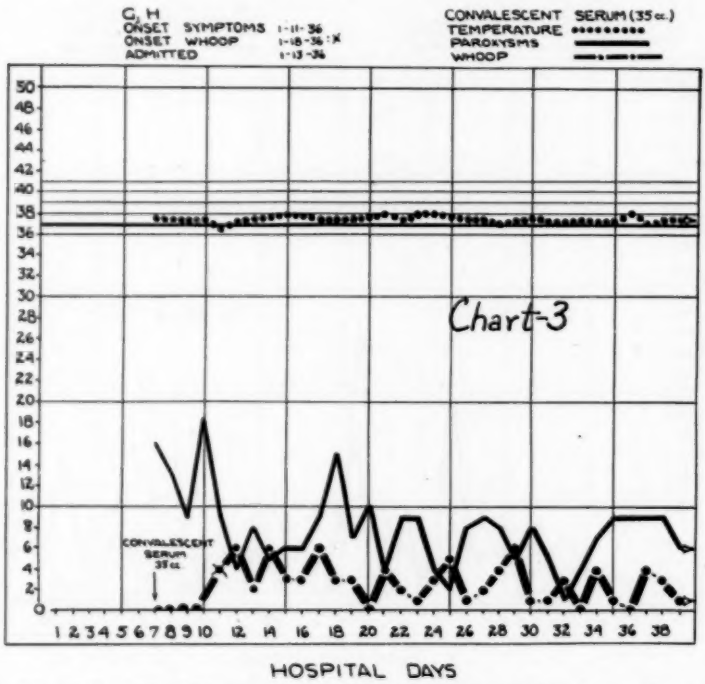


Chart 3.—G. H. This child was given 35 c.c. of convalescent whooping cough serum. There was no modification of the whooping attacks.

and actual fallacy of comparing alternate cases taken at random. Such controls are worthless. They may reflect mortality statistics but not degrees of disease severity. Conclusions based on comparative controls cannot be admitted. This disease is so variable that often parents and relatives do not know whether the patient has or has not had the disease; often, too, even the most intelligent and careful physician is hard pressed to make a positive diagnosis.

Controls can be furnished only by the patient himself. The child must be studied before and after a therapeutic agent is given, and the combined results obtained from hundreds of such studied cases may

give us some information. In addition, the death rate of treated children under two years of age could be compared to the average morbidity rate in that group for a number of years. Only then do we have information of value. A lack of consideration of the natural modifying factors is often the reason why statistics on this disease have to be interpreted with a great deal of caution and why most of them may safely be ignored.

It was decided to try out this mucoid material in treatment. In order to understand what might be expected one would have to call

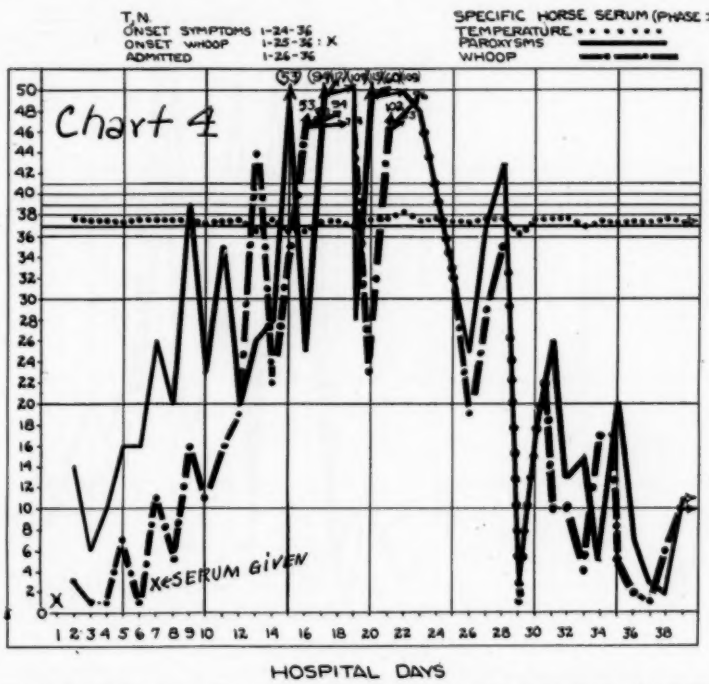


Chart 4.—T. N. was given 20 c.c. of horse serum intramuscularly (agglutinin titer 1:40,000 against freshly isolated organisms). If, as I believe, whooping cough patients are sensitized to *H. pertussis* bacteria, then any antiserum made from such a sensitizing antigen should aggravate rather than decrease the number of paroxysms. The results which followed the administration of antitoxin in this case strengthened that impression. This is one of twenty so treated patients, and all had like, although not so aggravated, responses.

attention to some general principles of immunity and protection. In many diseases it is the specific antigen that causes the disease effect seen in the human being. Some potent antigens, like diphtheria toxin which produces diphtheria in the human being, should not be injected into an individual during the acute stage of the disease because of the fear of synergizing the toxic effect of an already highly potent antigen. One must study the effects of an antigen, and its use should be properly

interdicted in the therapy of an acute infection should it be highly toxic to the human being. Such considerations do not prevent us from using *H. pertussis* mucoid antigen. It is relatively innocuous as far as the human being is concerned. Masses of specific material may be coughed up and yet the patient be relatively normal. It is only because it is so innocuous in its effect that we are justified in treating these cases during the active stages of the disease on the theory that specific antigen injected may create a specific antigen-antibody response sooner

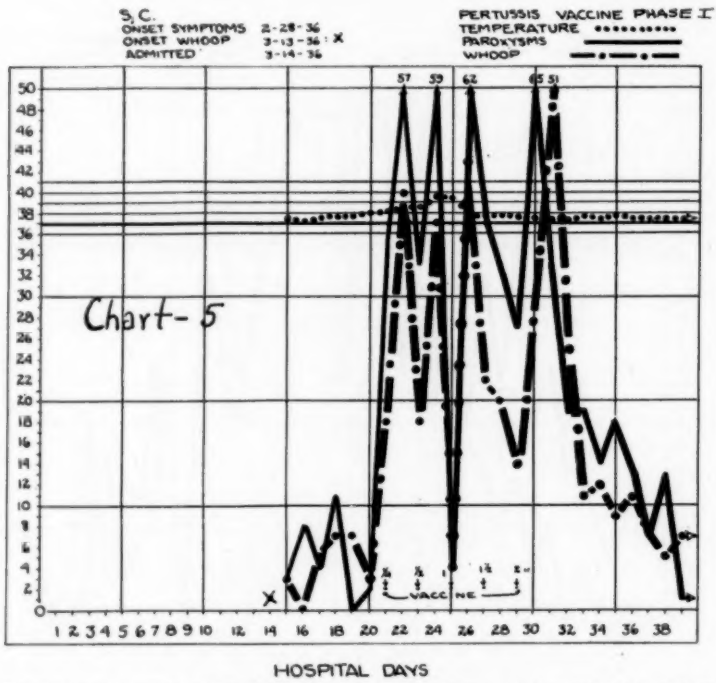


Chart 5.—S. C. was given freshly isolated organisms. If the antibody obtained from horses by injecting them with freshly isolated organisms aggravated the disease, the probabilities are that a child with whooping cough may actually have his paroxysms increased in number when the antigen itself is injected as was the case with this patient.

and thus shorten the length of the infection. Even a cursory familiarity with the problem of recovery from this infection makes it clear that the disease cannot be curtailed at once by the use of even specific antigens in active immunization. The only thing we can hope for is an amelioration of the symptoms or a lessening of the length of the disease. The sooner the injections are made after the initial exposure, the more obvious should be the results, which are measured in the patient himself in terms of the number of paroxysms and whoops present before and after therapy began.

At first, we tried alternate cases and pertussis mucoid material was injected as a vaccine into children ill with the disease. There seemed to be a shortening of the length of the attack, and a decrease in the number of paroxysms and coughs. The dose was too concentrated, 866 mg. of pertussis mucoid material in 1 c.c. of saline, and it contained a great number of phase IV organisms. Injections were often accompanied by local reactions, and some fever, especially if they had been made in an area containing a great deal of subcutaneous fat. If injected

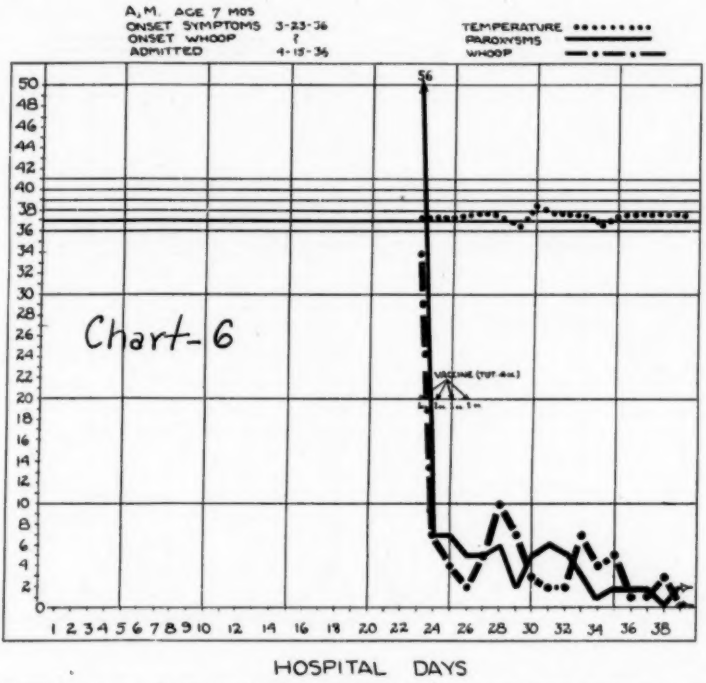


Chart 6.—A. M., P. W., and I. J. (Charts 7 and 8) were given pertussis mucoid material. A. M. received the vaccine late in the course of the disease, but the fall in the number of paroxysmal attacks after the administration of pertussis mucoid material was striking.

where there was too much fat, a low grade indurated area often developed which, though painless, would take from two to three weeks to absorb. The temperature reaction which followed these injections was as high as 101° F., and it never lasted longer than twenty-four hours. No one could foretell after which dose some local induration would occur, but usually after one reaction the subsequent injections were uneventful. There was no nausea, vomiting, or other generalized reactions. Twenty children were thus injected with massive doses of pertussis mucoid material with no untoward results.

The dosage was decreased to 40 mg. of pertussis mucoid material for 1 c.c. of saline. The product was purified, and the sensitizing phase IV organisms were omitted. Eighty children were then injected. In general, there were fewer paroxysms and whoops after the injections, and in a few instances, in which the injections had been given early enough, the whoops were almost entirely aborted. The local reactions were slight and, when present, localized. The best results, of course, were obtained when the injections were given immediately after ex-

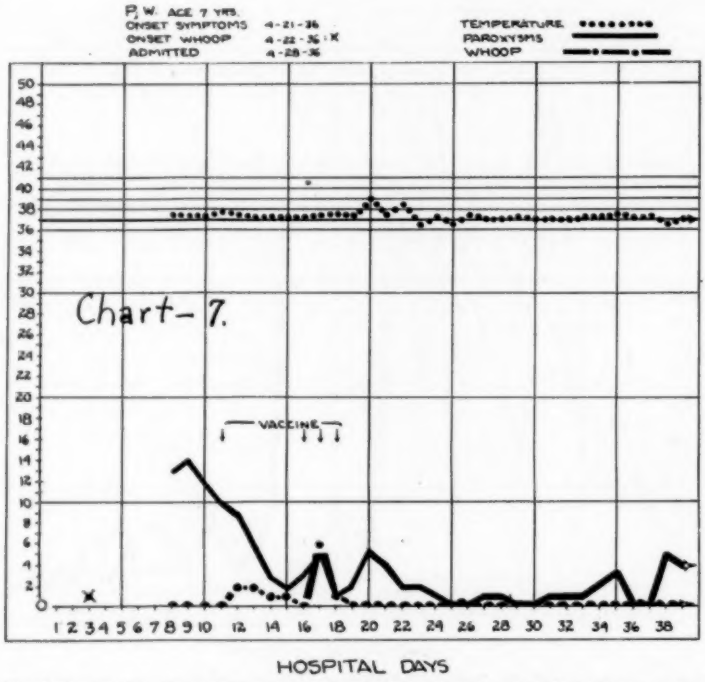


Chart 7.—P. W., also given pertussis mucoid material, showed a decrease in the number of paroxysms, and, although paroxysms were still present, the striking fact was that there were no whooping seizures.

posure. The slight amount of fever in the injected individual was due to some of the fixed phase bacilli. Recent isolations of the pertussis mucoid material by the author have been freed from bacilli, and this product did not give the reactions seen when bacteria were injected. Eighty children have been treated with suggestively good results. All of the patients were under three years of age. Many were infants as young as four weeks, and there was only one death from the disease.

The progress of whooping cough in the human being parallels in some measure the growth of the organisms in vitro. Freshly isolated or

disease-producing organisms are relatively innocuous as far as the human being is concerned, merely causing rhinitis. When the incubation and catarrhal stages are over and when the disease has reached the paroxysmal stage, we find that the patient has become sensitized to an antigen, probably an exotoxin produced during the growth of bacteria and referred to previously, for at this time skin tests made with these protein fractions were found to be positive, whereas there were no reactions to injections of the same antigen in a few of the same patients at the beginning of the disease attack. Since there was no reaction intradermally at the onset of the disease and later a definite local response

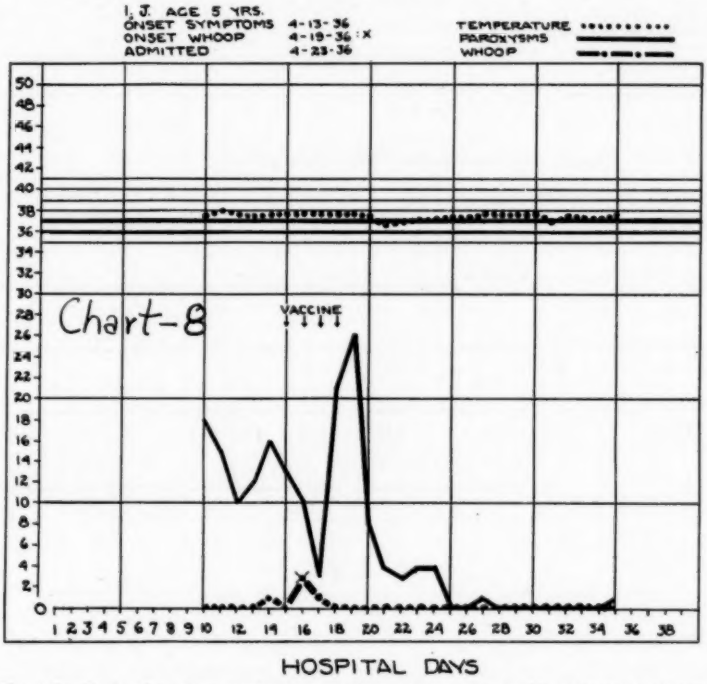


Chart 8.—I. J., also given pertussis mucoid material, like P. W., showed a decrease in the number of paroxysms, and, although the paroxysms were still present, the striking fact was the absence of whooping seizures.

at the beginning of the period of whooping, it would suggest that the individual has become sensitized to the bacterial product (probably an exotoxin) and that some of the paroxysmal reaction may be allergic in nature.

Coincident with the whoop, there is trouble in finding the disease-producing bacteria. The latter have become acclimated to the patient and may have changed their form or have become immersed in the sticky product of metabolic growth. They are no longer multiplying in an unfavorable medium, by reason of which they are now able to pro-

duce in the human being, as in the test tube, the pertussis mucoid metabolic material that is coughed out during the later paroxysmal and whooping stage of the disease.

The problem in one already ill with the disease would be to hurry the process of recovery by injecting the specific mucoid exudate. There would be no purpose in further sensitizing an individual with injections of bacteria of endoantigens made or obtained either from freshly isolated organisms or late phase IV organisms. Active artificial im-

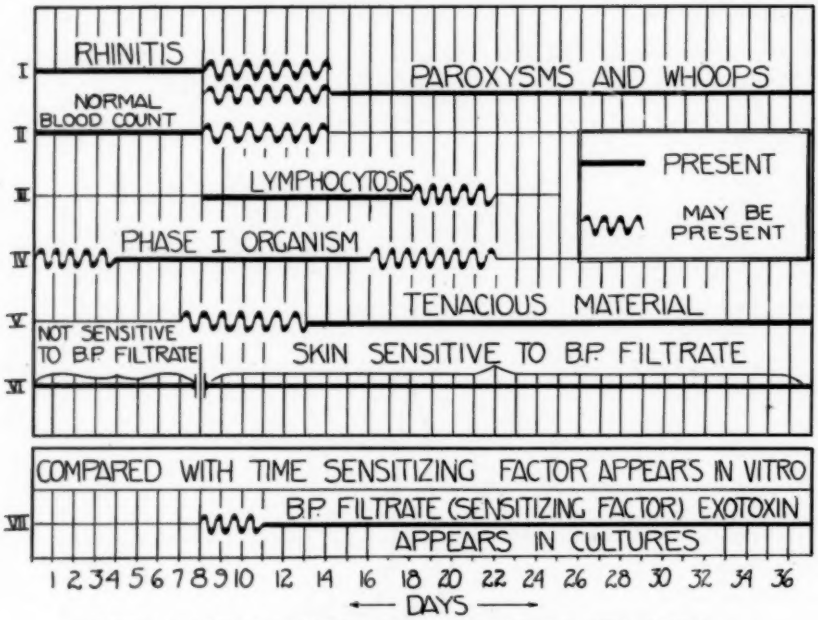


Chart. 9.—Clinical conditions appearing in whooping cough patients.

munity for individuals against this material of metabolic growth might be accomplished as in diphtheria by the injection of the metabolic material alone.

That these ideas have some foundation is seen from a study of charts of cases treated with various antigens. If the freshly isolated culture is merely a sensitizing agent, it would be expected that any serum made by injecting this factor into animals would yield an antibody antigen serum which, when used therapeutically, would aggravate the disease condition in the human being rather than alleviate it. Clinical experience seems to bear this out.

When pertussis mucoid material was used in the treatment of whooping cough, the results were suggestive, but definite conclusions cannot be drawn until hundreds of cases have been treated.

In short, our present work is still in the experimental stage. I merely raise some questions on the subject of whooping cough. These thoughts, if they accomplish no more, may make clear the fact that little is definitely known about the specific prevention or treatment of this disease.

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# STREPTOCOCCUS HEMOLYTICUS MENINGITIS

## With Recovery Following Mastoidectomy and the Intrathecal Administration of Lyophile Convalescent Scarlet Fever Serum

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WHILE streptococcic meningitis is a fairly common disease, only a few recoveries are recorded annually. It is therefore thought useful to add the details of another recovery to those already reported, particularly in view of the use of a new form of treatment.

In a tabulation of 284 cases of meningitis due to various organisms at the Children's Hospital of Philadelphia, 32 (11 per cent) were streptococcic, and none of the children recovered.[1] In 1935 Gray,[2] in reporting a case with recovery, made a survey of such cases in the literature up to that time. Since then several other cases with recovery have been reported.[3, 4] All these were differentiated by means of the recovery of streptococci in the spinal fluid.

### REPORT OF CASE

E. M., aged six years, female, white, was admitted to the Children's Hospital, on May 7, 1936, with both ears discharging, paroxysms of severe headache, rigidity of the neck, drooping left upper eyelid, and twitchings of the left side of the face.

The family history and past personal history were of no significance.

The present illness began five weeks before admission. At that time the girl developed fever, headache, and a diffuse, punctate rash, involving the body, but not the face. There was no sore throat, no vomiting, and no subsequent desquamation. There was no cough, coryza, or conjunctivitis. A diagnosis of German measles was made. The rash quickly disappeared, and the girl recovered and returned to school, although she had attacks of headache. About a week later, earache developed. On April 24 the left eardrum was bulging and was incised, allowing a free drainage of pus. In spite of this, irregular fever continued with periods of excruciating headache. The right ear looked innocent. The tonsils were greatly swollen, and the lymphatic glands at the angle of the jaw were enlarged and tender. On May 2 earache started on the right side, the drum bulged and was incised; this released seropurulent fluid under pressure.

X-ray examination by Dr. Ralph Bromer indicated increased density in each maxillary sinus, interpreted as pus in the left antrum and a polyp in the right; the frontal sinuses were clear, but the ethmoids and sphenoids showed increased density. Both mastoids showed symmetrical cell development with only slight haziness. With the ears freely draining, continuing headaches were attributed to the extensive upper respiratory infection. On May 5 the child vomited and complained of headache again; there appeared to be some stiffness of the neck. On May 6 this disappeared, and the child seemed much improved. On May 7 the stiff neck returned, the ptosis of the left eye appeared and drowsiness developed.

She was admitted to the hospital on May 7. She appeared to be a well-developed and well-nourished girl with marked prostration, decided deafness, flushed face,

drooping left eyelid, lateral nystagmus on occasion, and equal pupils reacting to light. Both ears were draining. There was no mastoid tenderness. The teeth were all sound; the tongue was heavily coated. The neck was tender and rigid. There were positive Kernig reflexes on both sides and a positive Brudzinski neck sign. There were bilateral abortive ankle clonus and rather active knee jerks. The heart and lungs were normal.

Spinal puncture was performed immediately and yielded yellow, cloudy fluid. The pressure was not measured but was apparently moderately increased. The fluid showed a high cell count, 3,240, all polynuclears, and with numerous intracellular and extracellular cocci, at first thought to be pneumococci, but proved by culture to be *Streptococcus hemolyticus.*

Two hundred cubic centimeters of 10 per cent dextrose in physiologic saline was given intravenously, and this was followed by 150 c.c. of citrated whole blood. Dr. E. H. Campbell operated upon both mastoids, making a thorough débridement, and laying bare the dura over the lateral sinuses. These appeared normal and no place of perforation was found.

On the next day the fluid was clearer, the pressure lower, the cell count lower, 1,790, and the fluid negative to both smear and culture. Treatment was then begun with convalescent scarlet fever serum, prepared by the lyophile process of Mudd and his coworkers.[5] The serum from recent convalescents is separated and instantaneously frozen in a special freezing mixture. It is then evaporated in the frozen state to almost complete dryness. It is called "lyophile" because of its avidity for solution; for example, the dried matter from 30 c.c. of human serum dissolved in two minutes in only 15 c.c. of distilled water. This amount was given intrathecally.

On the next day the fluid was again negative to smear and to culture and was much clearer, showing only 400 cells. However, on the fourth day, the fluid was much cloudier, and showed 2,112 cells. At first we attributed this to the effect of the serum, which, administered in double concentration, gave the child severe pains of the body and extremities, lasting for ten or fifteen minutes.

On the fifth day we were dismayed by cloudiness of the fluid again with 2,750 cells, and by the reappearance of the streptococcus in the culture. In spite of the discouraging appearance of the fluid, the patient herself seemed brighter and more comfortable.

From this time on, spasticity lessened, the sensorium brightened, the color and appetite improved, and the spinal fluid steadily improved. All improvement continued and on May 25, eighteen days after operation, the patient was discharged with only slight stiffness of the legs. She was seen six weeks later and was found to be perfectly normal in appearance and function. She was seen again five months after operation and was still perfectly normal.

This patient had, in all, eight spinal punctures. She had one intravenous glucose injection and five whole blood transfusions. She was given intrathecally three injections, 30 c.c. each, of lyophile convalescent scarlet fever serum, and one injection of 30 c.c. of the same serum intramuscularly. She had one injection intrathecally of 30 c.c. of lyophile pooled adult serum because we could not get the scarlet fever serum that day.

Table 1 shows a summary of the spinal fluid findings.

## COMMENT

Improvement began before the convalescent scarlet fever serum was begun, but there are some facts which make it possible that the operation alone was not responsible for the child's recovery. There was a *Streptococcus hemolyticus* recovered from the fluid and a staphylococcus from

TABLE I

SUMMARY OF SPINAL FLUID FINDINGS

| DATE | AMOUNT (c.c.) | PRESSURE | CHARACTER | CELLS | DIFFERENTIAL | SMEAR | CULTURE | PROTEIN | SUGAR | CHLORIDES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1936 | | | | | | | | | | |
| 5/ 7 | 5 | Increased | Cloudy | 3240 | All polynuclears | Gram + cocci | Strep. Hemol. | +++ | 0 | 700 |
| 5/ 8 | 2 | Low | Cloudy | 1790 | Nearly all polynuclears | 0 | 0 | +++ | | |
| 5/ 9 | 15 | Normal | Slightly cloudy | 400 | 61% polynuclears<br>28% lymphocytes<br>11% endocytes | 0 | 0 | +++ | 23 | 550 |
| 5/10 | 17 | Normal | Slightly cloudy | 2112 | Mostly endocytes | 0 | 0 | +++ | 0 | 467 |
| 5/11 | 25 | Normal | Slightly cloudy | 2750 | Mostly polynuclears | 0 | Strep. Hemol. 2-3 colonies | +++ | 0 | 614 |
| 5/13 | 18 | Normal | Slightly cloudy | 840 | 64% polynuclears<br>36% endocytes | 0 | 0 | 64.8 | 0 | 720 |
| 5/15 | 18 | Normal | Clear | 330 | Degenerated | 0 | 0 | +++ | + | |
| 5/20 | 9 | Normal | Clear | 46 | 12% polynuclears<br>57% lymphocytes | 0 | 0 | +++ | 38 | 710 |

the mastoid at operation. The organisms indeed disappeared from the spinal fluid the very day after operation but reappeared following a clouding of the fluid. These again disappeared after the serum therapy was continued. It is just possible that the meningitis occurred by convection from the sinuses rather than by way of the mastoids. It must be remembered that there were at first severely contaminated meninges and that recoveries have followed mastoidectomy in many cases, in spite of such severe contamination, without any such serum therapy. It is not our intention to claim that the serum used in this patient was responsible for her recovery; yet we have seen a good number of such patients, practically all of whom were operated upon, and all of whom died.

Particular notice should be given to the distressing trunk and extremity pain caused by the injection of a hypertonic serum. We believe this pain to be of osmotic origin because it disappeared in a few minutes as the serum became diluted. On May 11 we introduced serum containing about 12 per cent of protein. On May 13 the fluid removed contained only 0.064 per cent of protein. On the first removal after serum administration, the cell count did not increase, but on the second removal it contained a large proportion of endothelial cells, suggesting meningeal irritation. Later polynuclears became predominant when the culture became positive the second time, but as recovery advanced, lymphocytes appeared.

Sugar was absent from the spinal fluid on four of seven examinations and was low on two other examinations. The spinal chlorides were reduced, at one time as low as 467.

## SUMMARY AND CONCLUSIONS

Recovery from *Streptococcus hemolyticus* meningitis, apparently secondary to a severe upper respiratory tract infection with otitis and mastoiditis, is here reported. In addition to mastoidectomy and the usual supportive treatment, lyophile convalescent scarlet fever serum was administered intraspinally. The authors feel that while natural forces must be given credit for recovery in this particular instance, the serum used may have been of some aid in this process and may be well worth trying on other occasions.

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# CONGENITAL DUODENAL ATRESIA

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WASHINGTON, D. C.

RECENT articles have called attention to the occurrence of congenital intestinal obstruction in numbers large enough to justify its consideration in the differential diagnosis of conditions which cause persistent vomiting in infants.

The first case of congenital malformation of the duodenum to be cited in the literature was reported by Calder[1] in 1732. According to De Sanctis and Craig,[2] who have gone very thoroughly into the history of congenital intestinal obstruction, there have been 129 cases of duodenal atresia reported from Calder's time until 1929. In 1933 Ladd[3] reported 60 cases of intestinal obstruction at Children's Hospital in Boston and went rather completely into the etiology, diagnosis, and treatment of the condition. In June, 1935, Walker, Falkener, and Horsley[4] summarized the knowledge of the condition and made the plea that as two cases had appeared in their experience within a year's time, it should be considered among the commoner conditions. Collins and Kellogg,[5] and Donovan[6] have added three more cases of duodenal atresia to the rapidly growing list.

It is not necessary in this article to go into detail into the etiology, diagnosis, and treatment; for this no better references than the articles cited above can be given. To briefly summarize, then, the etiology may be intrinsic with reference to the gut, due to failure of the lumen to be reopened at the end of the twelfth week. It may be extrinsic and result from arrest in rotation of the viscera, malformation of the superior mesenteric vessels, congenital adenoma, kinking peritoneal band or an annular pancreas.

The diagnosis is based on the history, especially that of vomiting from birth, upon roentgen ray examination of the gastrointestinal tract, and upon the examination of the stools which will show the absence of keratinized cells and of lanugo hairs. The child with complete intestinal obstruction is very rarely alive after five days if no medical supportive or surgical measures have been taken. Pyloric stenosis, the condition with which it is most likely to be confused, appears later, usually after two weeks of age; the barium does not stop at the duodenum; and keratinized cells and lanugo hairs may be found in the stools.

From Children's Hospital, Washington, D. C.
Reported by courtesy of Dr. Frank Leech, Chairman, Medical Staff.
Read before monthly staff conference, Children's Hospital, Nov. 10, 1936.

The treatment is surgical; gastroenterostomy or a side-to-side duodenojejunostomy may be effected, depending upon the site and condition of the atresia. Preoperative parenteral administration of fluids and glucose is important.

Two cases of complete duodenal atresia which are reported here and one case of partial duodenal atresia which is being reported independently by Dr. Charles S. White and Dr. Edgar P. Copeland have been recognized at Children's Hospital within the period of six months.

CASE 1.—M. D., a white female infant, two weeks old, was brought to Children's Hospital on April 20, 1936. She had been born at term after a normal delivery. The birth weight was 3,400 gm. Soon after birth the patient became flushed and on the third day began to bleed from the nose and mouth. Blood was also found in the stools. The patient was given blood intramuscularly and the bleeding subsided somewhat. On the fifth day the patient started to vomit blood at thirty-minute intervals and was given coagulin and a blood transfusion, after which hemorrhage appeared to have been arrested. After the patient was ten days old she refused breast and bottle and vomited most feedings, nonprojectally.

On the evening of admission the skin was found to be flushed, and there had been vomiting of large amounts of new and old blood. The physical examination was otherwise essentially negative. A tentative diagnosis of hemorrhagic disease of the newborn was made. At 8 P.M. one ounce of evaporated milk—lactic acid formula—was given by gavage. At 10 P.M. the patient received a similar feeding but at this time became cyanotic. At 12 midnight the patient was given 75 c.c. of 5 per cent glucose in Hartman's solution by hypodermoclysis and oxygen continuously. At 1:30 A.M. the following day the patient vomited a large amount of bright blood and became markedly cyanotic. Artificial respiration was administered until 2:45 A.M. when respiration ceased.

Autopsy revealed a fairly well-nourished and well-developed white female, apparent age two weeks. The weight was 3,240 gm. and the length, 48 cm. A moderate amount of subcutaneous fat was present. The mediastinal and bronchial lymph nodes were enlarged.

The pleural cavity showed a recent adhesion formed by one of the lung abscesses described below. Adhesions were noted between the lobes of the left lung. No fluid was present. The lungs were of a deep red color with grayish circular areas representing abscesses scattered here and there. Crepitation was diminished throughout the greater portion of the tissue, and on section numerous abscesses, varying in size from 2 to 8 mm., were found. These abscessed areas were surrounded by pneumonic consolidation and their centers contained thick, yellowish gray pus.

The pericardial sac was found to be normal. The heart was normal in size, the foramen ovale and ductus arteriosus being patent.

The peritoneal cavity showed a red hemorrhagic area 1.5 cm. in diameter on the parietal peritoneum adjacent to the gallbladder. The liver was enlarged and somewhat congested. There were areas of a lighter color which were suggestive of an hepatitis. The wall of the gallbladder externally showed grayish and yellowish areas with a purple periphery. The wall was found to be thickened and abscessed on section. The interior of the organ was filled with a purulent brownish material. The cystic and common ducts were thickened, the latter being markedly so in the region of the ampulla of Vater, which was in the small portion of the duodenum below the atresia.

The spleen was congested and relatively firm. The stomach was somewhat dilated and its mucosa, very hemorrhagic. The pyloric orifice was markedly dilated, and the

first 3 cm. of the duodenum were much ballooned, its circumference measuring 6 cm. Its mucosa was likewise hemorrhagic. At a point 3 cm. from the pyloric orifice, the duodenum ended abruptly, there being no visible outlet. The remaining portion of the gut was found below the head of the pancreas; it was of very small caliber and contained a bile-stained material which, when examined microscopically, showed mucus, leucocytes, and bacteria. The appendix was small.

The mesenteric nodes were slightly enlarged. Possible evidence of pancreatitis was noted, and the adrenals showed a dark discoloration. The pyramids of both kidneys showed passive congestion. The retroperitoneal lymph nodes were slightly enlarged. The remaining abdominal viscera were normal.

CASE 2.—Baby B., a colored female infant, was admitted to Children's Hospital at 3:30 P.M., Oct. 22, 1936. She was born October 17, 1936, after a normal labor and delivery. The birth weight was estimated by the family physician to be 3,400 gm. The baby had been nourished at the breast since birth. Some water had been given. The father stated that she had vomited after each feeding, had refused to take water, and had not passed urine since birth.

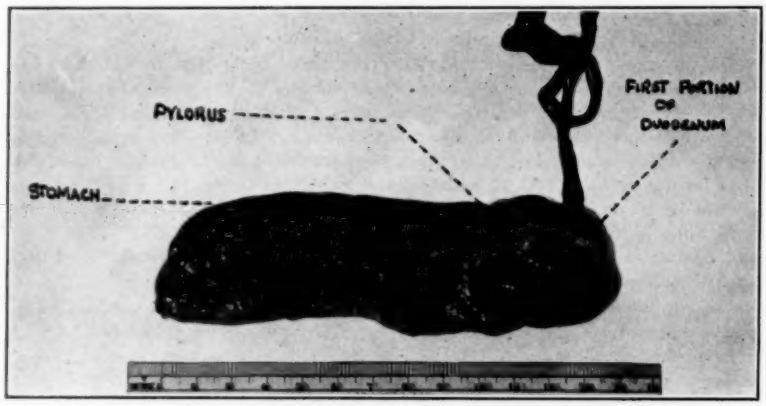


Fig. 1.—Case 2. Baby B., female. Showing opened stomach and dilated first portion of duodenum.

Upon examination the child was observed to be apathetic, crying feebly, and bleeding from the mouth and nose. The nutrition was poor, and cyanosis was present. The heartbeat was rapid, and the sounds were weak. The abdomen was soft, no peristalsis being visible. A tentative diagnosis of marasmus and possible obstruction was made.

At 6 P.M. 1 ounce of an evaporated milk formula was offered the infant. A small amount was taken. At 8 P.M. a small, green, smooth stool was passed. At 10 P.M. the patient was given another feeding, which she took poorly. It is not known whether this feeding was forced or not, but subsequently the patient became cold and the skin clammy. External heat was applied. At 12:45 A.M. 0.5 c.c. of coramine was administered intramuscularly. Fifteen minutes later 1 ounce of the formula was forced. The child subsequently vomited, the pulse became weak and rapid, the respiration was shallow, and the skin was cyanotic. At 4 A.M. the day after admission respiration ceased.

Autopsy showed an undernourished and premature-appearing colored female infant, weighing 1,700 gm. A small amount of subcutaneous fat was present. The pleural cavities showed a normal serous membrane and contained no free fluid. The

lungs were pink, but numerous areas of hemorrhage were present. The lower portions of both lungs were atelectatic. There was no evidence of pneumonic consolidation. The pericardial sac was found to be normal; the heart was normal in size, the foramen ovale and ductus arteriosus being patent.

The peritoneal cavity was normal in appearance. The liver was congested. The gallbladder was markedly enlarged and contained thick green bile. There was some thickening of the common and cystic ducts. The common duct entered the third portion of the duodenum, just below the atresia.

The stomach was dilated and the gastric mucosa hemorrhagic. The pyloric opening was slightly dilated, and the musculature moderately hypertrophied. The first portion of the duodenum, 3 cm. in length, was considerably ballooned and its

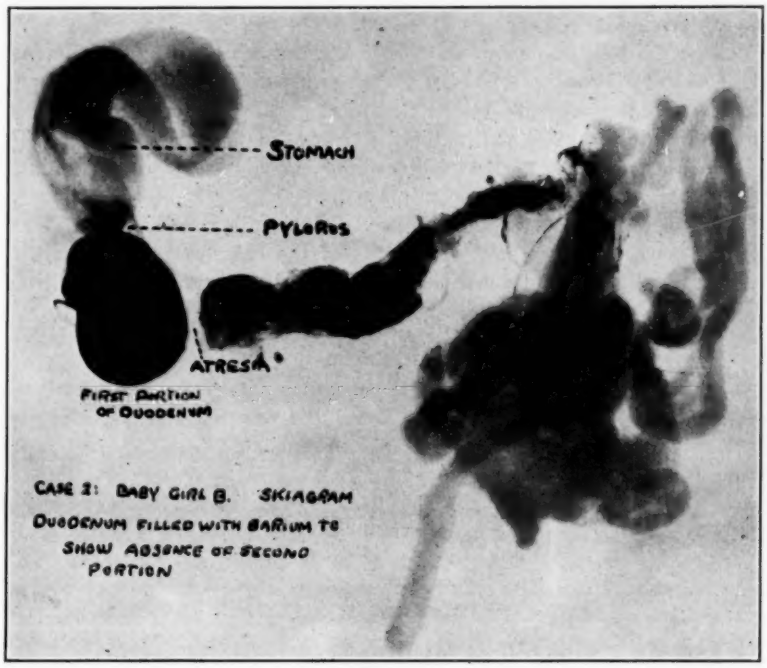


Fig. 2.

mucosa, markedly hemorrhagic. At a point 3 cm. from the pyloric orifice, the duodenum ended abruptly, no visible outlet being found. The remainder of the gut was found below the head of the pancreas being of small caliber and containing an intensely bile-stained material. The appendix was quite large but normal.

The left renal capsule contained a hemorrhage measuring 2 cm. in diameter. The remaining abdominal viscera were normal.

The identity of the clinical picture in these two cases is striking. It is significant to note that gavage was instituted in both cases and that immediately following this procedure hemorrhage and collapse ensued. The pneumonitis occurring in the first case is attributed to the aspiration of the vomited material.

The authors wish to suggest at this point that it be a rule not to institute gavage in an infant under two weeks of age with a history of vomiting from birth unless intestinal obstruction is definitely ruled out.

It is also interesting to note that in each case a patent ductus arteriosus and a patent foramen ovale were present.

## SUMMARY

Two cases of complete atresia of the second portion of the duodenum and one of partial atresia of the duodenum occurred within a six-month period at Children's Hospital.

The condition is common enough to warrant its consideration in the differential diagnosis of conditions causing vomiting in early infancy, and it would appear likely that similar cases have been treated at this and other institutions without being recognized.

The diagnosis is easily established by the history, x-ray examination, and examination of the meconium.

Treatment consists of immediate surgical intervention, which has proved successful in about two-thirds of the cases reported recently.

Gavage should not be instituted in infants with persistent vomiting from birth without definitely ruling out intestinal obstruction.

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# A CLINICAL STUDY OF THE APPLE DIET IN THE TREATMENT OF DIARRHEA IN INFANTS

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ALTHOUGH the treatment of infantile diarrhea by the empirical feeding of apples is said to date back at least twenty, and by some, forty years, it nevertheless must be regarded as one of the newer methods of therapy in the light of its use in the United States.

The origins, according to the German literature, are not based on scientific investigation and fact, but on two stories that smack considerably of being old wives' tales. The first story concerns that of an unidentified German sailor who was seized with a diarrhea while on an oriental expedition in about 1903. Since apples apparently were not found conveniently in the Orient, he substituted seventy or eighty ripe bananas which probably not only checked the diarrhea but produced obstipation.

The second bit of folklore about the apple diet is concerned with an incident occurring in a base hospital of the Central Powers during the Great War. Several dysentery patients had found it very expeditious to be ambulatory. An old apple tree grew in the back yard of the hospital, and approximately half of the patients consumed apples while the other half obligingly abstained, thus making an excellent if unwitting control group. The apple eaters, of course, made rapid recoveries in contrast to those who obeyed the doctor's orders.

Moro and Heisler, two German physicians, are generally given credit for having placed apple therapy on its first scientific basis. Since their time most of the literature on the subject has emanated from Germany, some from Vienna, and some from Paris.

We felt that this summer an opportunity was being afforded us to make a clinical study of the efficacy of the apple diet in the treatment of diarrhea. Our viewpoint must be that of the general pediatrics practitioner rather than that of the research specialist. Since most of the literature is written in a brightly optimistic vein we seized the opportunity to acquaint ourselves better with this hopeful method of treatment. This paper is a report of our observations and results.

## METHOD

Since no strict routine for treatment is outlined in any of the discussions, we adopted a routine that we thought corresponded to the ideas of other investigators. Unless otherwise stated, all patients

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on admission to the hospital underwent a twenty-four-hour period of starvation during which only water by mouth was offered. Parenteral fluids were supplied as necessary, and the mineral balance was maintained by the administration of calcium. If the nutritive state warranted, the baby received only water and apples the second twenty-four hours. The apples were given in doses of two teaspoonfuls every two hours. If we felt that the infant needed added nourishment, this was supplied in a skim milk or protein milk formula. Occasionally we added carbohydrate either in the form of lactose or imperial granum.

In infants the transition diet from starvation to a normal diet consisted of protein milk with slowly increasing amounts of carbohydrate. In older children we gave cottage cheese, gelatin, beef broth, potatoes, and rice gruel and very gradually replaced the carbohydrates.

In a certain number of infants no amount of coaxing, patience or skill could make them take apples in the prescribed amount. We sweetened the apples with lactodextrin or saccharine and even mixed in ripe mashed banana pulp but with little success. Winters and Tompkins have suggested that pectin is the potent factor in the apple diet. We are obliged to the dietitian of the hospital for the suggestion that pure pectin could be obtained cheaply as ordinary commercial certo. Certo itself has a very tart taste and is no more palatable than the apples. Following the ideas of Winters and Tompkins, we mixed the certo with agar-agar and water and flavored with peppermint water. The result was a pectin-agar mixture of the consistency of gelatin. This was used in a small number of cases. No attempt was made to compare its value with that of scraped raw apples.

## CLASSIFICATION

We have adopted one classification of the etiology of diarrhea so that we may better evaluate our results.

A. Infectious

1. Enteral infections. In this group we have placed the specific enteral infections, such as typhoid fever and dysentery and those of the salmonella group.
2. Parenteral infections. In this group are included those diarrheas associated with aparenteral infections such as otitis media, acute coryza, impetigo, and bronchitis.

B. Irritative-fermentative. In this group we included those diarrheas caused by dietary indiscretions, spoiled foods, and dirty milk and from bacilli entering to the gastrointestinal tract through dirty utensils used in preparing milk.

## RESULTS

A total of ninety cases was studied, forty of which were followed in the dispensary and the remainder in the hospital. Seven infants were admitted in a moribund condition with the classical picture of acute alimentary intoxication as described by Finklestein. All of these patients expired within twenty-four hours despite the administration of parenteral fluids and supportive measures. Four patients with proved dysentery and one infant with what clinically resembled dysentery expired in spite of the administration of apple diet, specific serum, transfusions, and supportive measures.

Seventeen cases were classified as belonging in the fermentative-irritative group and were treated by the apple regime. In these infants the mean number of days of illness prior to admission was four. All were having from ten to sixteen green liquid mucous stools per twenty-four-hour period. Occasionally bloody stools were found in this group. Most of these patients were dehydrated, and all were considered to be seriously ill.

The average length of time that apple was given was from seven to eight days, with the appearance of the first formed stool occurring on the fifth to the eighth day. In this group we recorded one death.

Six cases considered to have the same etiology were treated by a starvation period of twenty-four hours followed by a protein milk formula. These cases were also considered to be severe in nature. No deaths occurred in this group.

Eleven infants with diarrheas considered to have an origin in a parenteral infection were treated with scraped raw apple. In general, these cases were less severe than those in the above group. Here again apples were given for seven days with the first formed stool appearing on the fifth to the eighth day. One infant in this group died.

Four cases of parenteral diarrhea were treated by starvation followed by protein milk formulas. All four infants recovered.

In all, twenty-eight infants, excluding the dysentery patients, were treated by apple diet, and twelve by starvation followed by protein milk. All presented similar clinical pictures, and the results of the therapeutic effort in the different groups showed no striking differences.

The dispensary cases were followed with great difficulty. On reviewing the charts, we found that a large number of infants had not returned after one or two visits. Since this is practically the only pediatric dispensary in Columbus, we were forced to conclude that the patients had improved. This was subsequently proved to be correct by a fair number of follow-ups. The results in the dispensary were far more gratifying than those in the hospital cases. Naturally the diarrheas were less severe. As far as possible, the diarrhea pa-

TABLE I

| CASE | AGE (MO.) | DURATION ILLNESS BEFORE ENTRY (DAYS) | CHARACTER OF STOOLS | AVERAGE NO. OF STOOLS | APPLE (DAYS) | FIRST FORMED STOOL (DAY) | DIAGNOSIS | RESULT |
|---|---|---|---|---|---|---|---|---|
| 1 | 42 | 4 | Gr. liq. mucous | 8-10 | 12 | 8 | Fermentat. | Recovery |
| 2 | 30 | 1 | Yell. gr. liquid | 10 | 7 | 5 | Fermentat. | Recovery |
| 3 | 12 | 21 | Liquid br. mucous | 6-8 | 4 | 4 | Fermentat. | Recovery |
| 4 | 1½ | 3 | Yell. liq. | 8-10 | 8 | 6 | Fermentat. | Recovery |
| 5 | 13 | 3 | Yell. liq. | 6-8 | 4 | 3 | Fermentat. | Recovery |
| 6 | 7 | 4 | Gr. liq. | 6-8 | 10 | 8 | Fermentat. | Recovery |
| 7 | 5 | 9 | Gr. liq. mucous | 14-16 | 16 | 14 | Fermentat. | Recovery |
| 8 | 7 | 2 | Gr. liq. mucous | 12-14 | 6 | 5 | Fermentat. | Recovery |
| 9 | 2 | 1 | Gr. liq. mucous | 10-12 | 8 | 7 | Fermentat. | Recovery |
| 10 | 36 | 1 | Gr. liq. bloody | 12-14 | 9 | 10 | Fermentat. | Recovery |
| 11 | 4 | 5 | Gr. liq. bloody | 10-12 | 9 | 8 | Fermentat. | Recovery |
| 12 | 13 | 4 | Gr. liq. mucous | 8-10 | 5 | 6 | Fermentat. | Recovery |
| 13 | 4 | 2 | Yell. liq. muc. bloody | 15-20 | 8 | 8 | Fermentat. | Recovery |
| 14 | 4 | 3 | Yell. liq. muc. bloody | 18-20 | 2 | 0 | Fermentat. | Death |
| 15 | 8 | 2 | Gr. liq. muc. bloody | 12-14 | 2 (pectin) | 8 | Fermentat. | Recovery |
| 16 | 17 | 2 | Gr. liq. mucous | 10 | 5 | 5 | Fermentat. | Recovery |
| 17 | 7 | 13 | Gr. liq. mucous | 10 | 12 Protein milk | 11 | Fermentat. | Recovery |
| 18 | 36 | 5 | Gr. liq. mucous bloody | 10 | | 8 | Fermentat. | Recovery |
| 19 | 1½ | 7 | Gr. liq. mucous | 15-20 | | 4 | Fermentat. | Recovery |
| 20 | 3 | 4 | Gr. liq. mucous | 20 | | 3 | Fermentat. | Recovery |
| 21 | 4 | 2 | Gr. liq. mucous | 16 | | 5 | Fermentat. | Recovery |
| 22 | 3 | 4 | Gr. liq. mucous | 10-12 | | 5 | Fermentat. | Recovery |
| 23 | 9 | 7 | Gr. liq. mucous | 10 | | 8 | Fermentat. | Recovery |
| 24 | 12 | 2 | Gr. liq. mucous bloody | 17 | 2 (pectin) | 5 | Parenteral upper resp. infection | Recovery |
| 25 | 15 | 21 | Gr. liq. | 6-8 | 2 | 8 | Upper resp. infection | Recovery |
| 26 | 8 | 4 | Gr. liq. mucous bloody | 10-15 | 7 | 0 | Pneumonia | Death |
| 27 | 7 | 3 | Gr. liq. mucous | 6-8 | 6 | 5 | Otitis med. | Recovery |
| 28 | 30 | 5 | Gr. liq. mucous bloody | 7-9 | 8 | 6 | Upper resp., otitis med. | Recovery |
| 29 | 9 | 2 | Gr. liq. mucous | 6-8 | 5 | 4 | Furuncle, nose | Recovery |
| 30 | 7 | 3 | Gr. liq. mucous | 6-8 | 10 | 8 | Pertussis | Recovery |
| 31 | 8 | 14 | Gr. liq. bloody | 14 | 12 | 10 | Otitis med. | Recovery |
| 32* | 1½ | 1 | Gr. liq. mucous | 4 | 3 | 3 | Upper resp. infection | Recovery |
| 33* | 1¼ | 1 | Yell. liq. | 6 | 5 | 3 | Upper resp. infection | Recovery |
| 34 | 9 | 2 | Gr. liq. mucous | 6-8 | 6 | 4 | Otitis med. | Recovery |
| 35 | 2 | 3 | Gr. liq. mucous | 6-8 | Protein milk | 6 | Otitis med. | Recovery |
| 36 | 3½ | 4 | Gr. liq. mucous | 12 | Protein milk | 4 | Upper resp. infection | Recovery |

*Premature twins (Cases 32 and 33)

TABLE I—CONT'D

| CASE | AGE (MO.) | DURATION ILLNESS BEFORE ENTRY (DAYS) | CHARACTER OF STOOLS | AVERAGE NO. OF STOOLS | APPLE (DAYS) | FIRST FORMED STOOL (DAY) | DIAGNOSIS | RESULT |
|---|---|---|---|---|---|---|---|---|
| 37 | 2½ | 2 | Gr. liq. bloody | 5-7 | Protein milk | 4 | Upper resp. infection | Recovery |
| 38 | 2 | 3 | Gr. liq. mucous | 6 | Protein milk | 5 | Upper resp. infection | Recovery |
| 39 | 9 | 28 | Gr. liq. mucous | 15-20 | | 0 | Aliment. intox. | Death |
| 40 | 2 | 5 | Gr. liq. mucous | 20 | | 0 | Aliment. intox. | Death |
| 41 | 8 | ? | Gr. liq. mucous | 18 | | 0 | Aliment. intox. | Death |
| 42 | 8 | 3 | Gr. liq. mucous | 30 | | 0 | Aliment. intox. | Death |
| 43 | 12 | 2 | Gr. liq. mucous | 10 | | 0 | Aliment. intox. | Death |
| 44 | 8 | 14 | Gr. liq. mucous | 20 | | 0 | Aliment. intox. | Death |
| 45 | 2½ | 4 | Gr. liq. mucous | 10 | | 0 | Aliment. intox. | Death |
| 46 | 24 | 1 | Gr. liq. mucous bloody | 15 | 2 | 0 | Dysentery | Death |
| 47 | 24 | 30 | Gr. liq. mucous bloody | 20 | 11 | 0 | Dysentery | Death |
| 48 | 36 | 7 | Gr. liq. mucous bloody | 10 | 16 | 0 | Dysentery | Death |
| 49† | 12 | 7 | Gr. liq. mucous bloody | 10 | 20 | 0 | Dysentery | Death |
| 50 | 5 | 4 | Gr. liq. mucous bloody | 10 | 7 | 0 | Dysentery | Death |

†Clinical diagnosis of dysentry (Case 49)

tients were alternately tried on the apple regime and the starvation and skim milk regime. The great majority showed marked improvement in two to four days, regardless of what mode of therapy was followed.

## DISCUSSION

Early in the summer we reviewed the available literature regarding this mode of treatment. The unanimity of good results was so striking that it appeared that the apple diet might be added to the list of specifics in medicine. Moro himself reported excellent results in all types of infantile diarrhea, including dysentery and typhoid fever. Beckman in his recent text states, "Its success has been so great that it will undoubtedly replace most of the other methods of handling these cases."

"Excellent results were obtained in cases of acute and chronic dyspepsia, epidemic dysentery, Herter's infantilism, and in one case of typhoid fever," states Mignot in a French journal of medicine.

Mouzon, writing in *Presse Medicale*, says, "The chief field of Moro's apple diet is in the acute enteritides of infancy. It also acts favorably on dysentery due to Flexner's bacillus and Y bacillus and that due to the colon bacillus. The colic and tenesmus cease in one to two days, and the fever drops."

And finally we quote Siegfried Wolff writing in a German journal, "Five cases of clinical dysentery with innumerable mucosanguinolent stools, tenesmus, and fever were cured within twenty-four hours in the manner described."

These brilliant results we cannot match. All of our patients with dysentery expired despite apple diet, specific serum therapy, repeated transfusion, and all other methods at our disposal.

In perusing the results of the apple diet on the ordinary enteritides of infants, we found that even the most pessimistic of the observers states that all patients responded to the treatment by having formed stools no later than the fourth day of the diet while most patients responded within twenty-four to forty-eight hours.

Tompkins of the University of Indiana, whose reports are by far the most conservative, states, "In most cases formed stools appeared on or before the fourth day." In our series we found that the formed stools appeared on the average in five to eight days and that since usually the infant had one or two formed stools that day and several liquid stools, one could hardly state that the appearance of the first formed stool heralded the cessation of the diarrhea.

Furthermore, we were unable to find any appreciable difference in response between those infants on the apple diet and those on the other forms of therapy tried. In both series of cases it was a long and drawn-out battle in most instances in which the child began to have physiologic activity of the digestive tract only after one or two weeks.

In the dispensary cases again no marked difference of response was noted in the two modes of treatment. Almost all infants responded as well to a twenty-four-hour period of starvation followed by very gradual resumption of carbohydrates and fats in the diet as they did to the feeding of raw scraped apples. On the average, it was only two days before the child was having formed movements.

Numerous theories have been advanced as to the therapeutically potent factor in the apple diet. Moro, himself, believes that one deals here chiefly with a mechanical cleansing action of the spongy apple mass on the intestines with an absorption of some of the toxins by the apple pulp; he also believes that the tannic acid content of the apples plays some rôle. Heisler assumes that the acids contained in the apple play the important rôle in that they change the reaction of the intestinal

contents. A similar view was expressed by Kohlbrugge, who believes that equally good results could be obtained by the administration of citric acid.

Malyoth believes that pectin, which is present in apples to the extent of 5 per cent, is the most important factor and this view has been revived and enlarged upon by Winters and Tompkins.

## CONCLUSIONS

Rest of the affected part is the basis of therapeutics. From a review of the various methods used in the treatment of diarrhea, it seems to us that the whole matter resolves itself down to the one fundamental principle of rest to the gastrointestinal tract. In all procedures there is a period of starvation followed by a period of administration of a nonirritative, bland diet, low in carbohydrate and fat. Parenteral fluids are administered as necessary in a supporting rôle. We believe that any rôle that apples play in the treatment of diarrhea depends not on their chemical nature but on their physical properties.

## SUMMARY

In the past summer ninety cases of diarrhea, fifty in the hospital and forty in the dispensary, were studied, and an attempt was made to compare the results of apple therapy with other methods in the treatment of diarrhea.

1. Apple diet was of no value in the treatment of dysentery.

2. In both mild and severe types of diarrhea in infants the results obtained with apple therapy were no better than those obtained in any other type of treatment.

3. Any beneficial results obtained from the use of apple diet were due to the period of starvation and the rest induced in the gastrointestinal tract by the bland nonirritating qualities of the apples.

4. The care of diarrheas depends on rest for the gastrointestinal tract, parenteral fluids, supportive measures, and maintenance of the mineral balance.

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# BRAIN TUMORS FROM THE PEDIATRICIAN'S VIEWPOINT

## With a Report of Ten Cases

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THE purpose of this report is to add to the published records of brain tumors in children ten cases which have been proved by operation or autopsy at the Philadelphia General Hospital and studied pathologically by the Division of Neuropathology. These include three cases of unusual involvement of the nervous system by malignant disease.

With the advances in neurosurgical technic and management of brain tumors resulting in a decrease of operative mortality, the burden of responsibility for an early diagnosis in these patients is being pushed back upon the general practitioner and the pediatrician. Most pediatricians have not had the specialized training necessary for accurate localization of brain tumors or for determining which patients warrant surgical intervention; however, it is the pediatrician who must recognize the early symptoms and signs which suggest the possibility of such a lesion's being present. Once it is suspected and steps are taken to verify the diagnosis, the pediatrician's duty is done.

There are several factors operating in the anatomic and physiologic make-up of a child which make the diagnosis of brain tumor a difficult procedure. This is especially true of those tumors occurring in infancy. Gross,[2] in reporting nine cases of brain tumor in patients under two years of age, has emphasized the significance of a yielding cranium in this age group before cranial sutures have permanently closed. This yielding of the cranium to a gradually increasing intracranial volume due to the growth of the tumor itself, or to developing hydrocephalus caused by pressure of the tumor on a part of the ventricular system, prevents the intracranial pressure from reaching the point necessary to give symptoms. Consequently by the time symptoms occur in infants, the intracranial pathology is usually far advanced. At autopsy Gross found hydrocephalus present in all nine of his cases, and in seven the rapid enlargement of the head was noticed by the parents.

The difficulty of testing sensation, the practical impossibility of obtaining visual fields, and the indefinite reflex response of young children add to the diagnostic problem.

Even when the intracranial pressure has increased past the point where the cerebral circulation is able to compensate for it, the symptoms of vomiting and convulsions, which are the ones chiefly present,

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are not at all specific of a diagnosis of brain tumor. The fact that so many other more common disturbances of infancy also manifest themselves by vomiting or convulsions is very misleading, but in these cases the etiology is usually apparent or becomes so before the symptoms have continued very long.

In older children the skull is more of a closed cavity and any increase in its contents will usually be accompanied by an increase in intracranial pressure, the symptoms and signs of which will manifest themselves earlier in the course of the tumor's growth than they do in infancy. Even though in this older age group the diagnosis is not so difficult, these cases are often passed over for weeks or months before a brain tumor is suspected.

Whereas in infants a knowledge of the anatomy and physiology in relation to the intracranial growth is important, in older children it is more necessary to know the incidence of the different types of tumor peculiar to childhood.

Cushing,[1] whose experience with the brain tumors of childhood is more extensive than that of any other surgeon in the country, has summarized 154 cases occurring in the preadolescent age group. As to location, he found that twice as many tumors originated in the cerebellum as in the cerebrum, whereas in adults five times as many were located in the cerebrum as in the cerebellum. Of brain tumors in all age groups he has found 20 per cent to be meningiomas and acoustic tumors and another 20 per cent pituitary adenomas; yet these two groups occur very rarely in childhood. Seventy-five per cent of his 154 preadolescent patients had gliomas; the next most frequent group included congenital tumors chiefly arising from an anlage of Rathke's pouch and a few tuberculomas. The glioma group consisted of spongioblastomas, medulloblastomas, and astrocytomas in order of increasing frequency of occurrence. Thus in children of the preadolescent period having symptoms suggestive of brain tumor, there is a 2 to 1 chance that the tumor will be cerebellar in location and a 3 to 1 probability that it will be gliomatous in nature.

### SUMMARY OF CLINICAL FINDINGS IN 10 CASES

Eight of the cases here reported were between the ages of two and fifteen years, only two being under two years of age. Although diagnostic criteria are somewhat different in infancy and childhood as noted above, still a summary of the symptoms found in this cross-section of a pediatric service rather than from a specialized group is of value in pointing out the clinical findings which in children suggest the possibility of a brain tumor.

Eight patients had vomiting, the duration of which varied from ten days to one year before admission to the hospital. This vomiting was associated with headache in six. Nothing characteristic was

noticed in the vomiting except that in the majority of cases it was projectile in type. There was no apparent relationship to meals, the most important characteristic being its persistence in spite of symptomatic treatment and the impossibility of discovering the presence of any of the usual causes of vomiting. Generalized convulsions, having no peculiar characteristics, were present in only three cases and had been present from the beginning of the illness.

Enlargement of the head due to internal hydrocephalus was noticeable in only two instances; yet at autopsy internal hydrocephalus was found in six brains.

Definite neurologic localizing signs were present in eight. This high percentage was probably due to the fact that on admission these patients all had far advanced lesions.

In spite of the fact that all these patients were hospitalized and there was opportunity for complete study, only seven had eyeground examinations. Of these, only five showed evidence of choking of the disks. It is worth noting here that the differences in the severity and duration of increased intracranial pressure had their corresponding variations in the eyegrounds. Beginning with engorgement of the veins as the earliest sign of increased pressure, there followed in succession blurring of the disk margins, choking, hemorrhage, occasionally exudate, and finally optic atrophy. However, it must be mentioned that if intracranial pressure increases very slowly, little or no choking may be present. This is illustrated in Case 1.

Ventriculograms were made on two individuals, the results showing positive evidence of tumor in both instances—the one having dilated ventricles, the other a large cyst in the temporal lobe just lateral to the ventricle.

The inability of the ordinary flat x-ray plate of the skull to make a diagnosis of cerebral neoplasm is demonstrated by the fact that of seven patients so examined reports were negative in three, and the reports in four consisted of such diagnoses as "convolutional atrophy," "depressed area on inner table," "thinning of bones." Although these findings are quite indefinite they do suggest further lines of investigation.

CASE 1.*—J. M., aged six years, white. Convulsions began at the age of fourteen months, often several a day but only one every few weeks recently. For the past four years the parents noticed weakness of right arm and both legs. The child was able to walk but had difficulty rising to a sitting position.

*Physical Examination on Admission.*—Speech was slow and poorly formed. The child responded slowly to questions. The head was larger than normal (circumference 53.7 cm.). The right pupil reacted better to light than the left. Eyegrounds were negative. The left side of the face was flatter than the right; there were frequent grimaces, occasional muscular twitchings, general hyporeflexia; and weak grip. Gait was ataxic, and there was ataxia of the upper extremities. The intelligence quotient showed a mental age of five years. Blood pressure was 105/62.

*Service of Dr. J. Blechschmidt.

*Laboratory Findings.*—Spinal fluid pressure was 8 mm. of mercury; Queckenstedt reaction, normal; chlorides, 692; colloidal gold curve, 1111122100. Blood Kahn test was negative; sugar, 85; urea nitrogen, 14. The red blood cells numbered 5,100,000; white blood cells, 10,200; polymorphonuclears, 69 per cent; lymphocytes, 27 per cent; monocytes, 4 per cent. The electrocardiogram was normal. X-ray plates of the skull showed bones thinner than normal, convolutional atrophy; and posterior clinoids definitely sharpened. Ventricular puncture was performed and was followed by ventriculogram which showed the cerebrum to be practically all lateral ventricles. One day later patient died with terminal bradycardia.

*Autopsy Findings.*—Marked internal hydrocephalus. Firm tumor mass involving vermis and right cerebellar hemisphere, tegmentum of upper half of pons and a large part of the basis pontis.

*Histologic Diagnosis.*—Unipolar spongioblastoma.

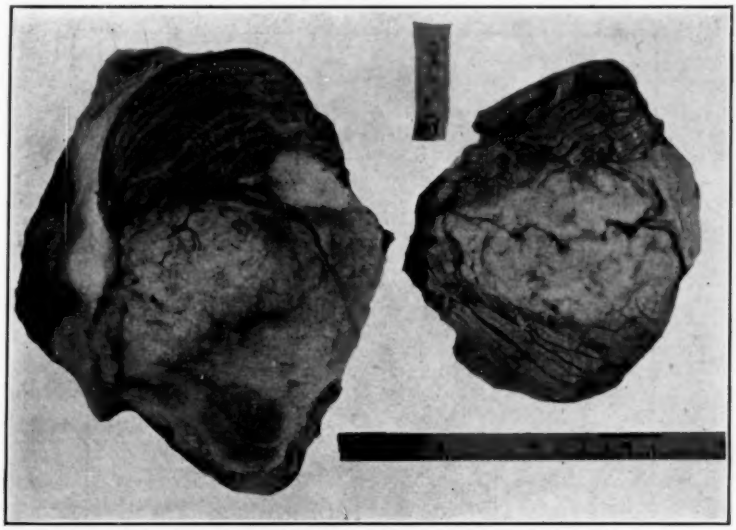

Fig. 1.—Case 1. Unipolar spongioblastoma. Cross-section showing involvement of vermis right cerebellar hemisphere and invasion of the pons.

CASE 2.*—F. K., aged fifteen years, white. On the day before admission the patient struck his head in the frontal region and complained of abdominal pain and headache followed by vomiting. A few hours later the patient became stuporous, with a slow irregular pulse.

*Physical Examination on Admission* (January 25).—No positive neurologic findings were noted, but the patient was dazed and had tenderness over right frontal area. Blood pressure was 100/70; temperature, 98.8° F.; pulse, 60; respiration, 23. Spinal fluid pressure was 17 mm. of mercury. On January 26 the pulse was still 60; there were right facial weakness, positive Hoffmann's sign on left side, sluggish abdominal reflexes, equivocal Babinski sign on right side, and choked disks 3 D, right eye; 2 D, left eye. The pulse continued to be slow and the headache persisted. On January 29 choked disks 4 D, right eye, 3 D, left eye were noted; there were right central facial weakness and slight deviation of the tongue to the right.

*Service of Dr. F. C. Grant.

The blood urea nitrogen was 22; spinal fluid sugar, 60; chlorides, 728; globulin, slight trace; Wassermann test, negative; colloidal gold curve, 0111000000.

The x-ray plate of the skull showed convolutional atrophy.

On January 30 both disks were choked 5 D with more exudate and hemorrhage than before. On February 4 there were bilateral Kernig sign and equivocal Babinski reflex on the left. On February 6 right external rectus was weak. There was choking 2 D, right eye, and 4 D, left eye. On February 8 there was vomiting. On February 9 the visual fields were normal. Trephinement was performed over both frontal areas: right, normal; left, tumor. Biopsy was taken. The operative procedure was carried out by Dr. F. C. Grant. On February 10 the patient was stuporous. Left temporoparietal bone flap exposed large cortical infiltrating tumor near midline in left prefrontal area. Tumor was removed with Bovie knife. On February 11 the patient died.

*Histologic Diagnosis.*—Medulloblastoma cerebri.

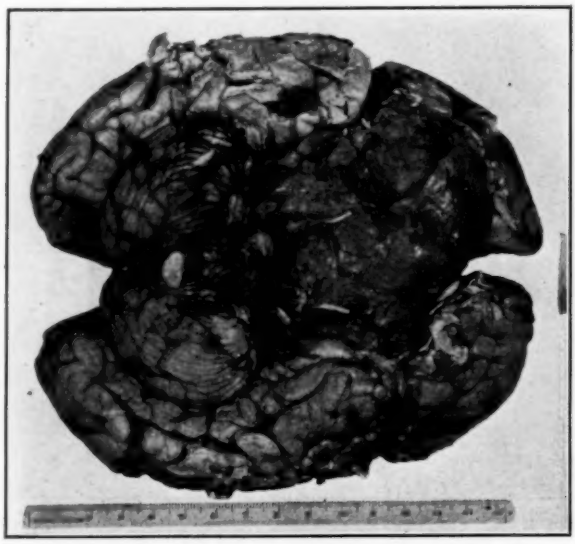

Fig. 2.—Case 3. Swannoma, an enormous fleshy tumor in the midline obliterating all the basal ganglia. Marked internal hydrocephalus.

CASE 3.*—L. R., aged seventeen months, white.

In February, 1932, the child vomited frequently. In March, 1932, the patient had pertussis, was sick for four months, and then became blind. In July, 1932, the head was becoming large. Vomiting which had become less frequent became worse, and the eyesight, which had partially returned, became more impaired together with partial deafness in February, 1933 (six weeks before admission), and these symptoms persisted.

*Physical Examination on Admission* showed enlarged head (circumference 48 cm.), bulging fontanels; wide cranial sutures; conjugate deviation of eyes to right. Pupils did not react to light, and the child was apparently blind and deaf. Superficial reflexes were absent, and the deep reflexes were increased.

*Service of Dr. J. W. Holmes.

A few days later there were Magnus and de Kleign neck reflexes present, clonic convulsions, muscular twitchings, rotatory nystagmus, optic atrophy, and a cisternal fluid pressure of 10 mm. mercury.

Death occurred shortly after admission.

*Autopsy Findings.*—Large soft brain with marked internal hydrocephalus. Enormous fleshy tumor in midline obliterating all the basal ganglia. Also small tumor nodules projecting from left cerebellar hemisphere at margin of cisterna magna.

*Histologic Diagnosis.*—Swannoma (central neurinoma).

CASE 4.*—R. W., aged four years, white. Five months before admission the child had slight head injury and two months later began to have periodic attacks of severe headaches followed by vomiting and convulsions. These attacks became more frequent and occurred daily for one week prior to admission. On the day before admission to the hospital the patient had an attack and became stuporous after the convulsion, which persisted.

*Physical Examination on Admission.*—The child was poorly nourished. There was continuous tonic convulsion, with lead-pipe rigidity. The eyes were fixed and scalp veins engorged. The left pupil was more dilated than the right and more sluggish in reacting to light. There was conjugate deviation of the eyes to the right and bilateral choked disks of 4 D with hemorrhage in the left. There was marked nuchal rigidity. Râles were present over both lungs. All superficial reflexes were absent and all deep reflexes increased. There was a continuous bilateral Babinski reflex. Slight Kernig and Brudzinski signs were noted.

The spinal fluid pressure was 50 mm. of mercury. Red blood cells numbered 4,800,000, with hemoglobin content of 100 per cent; white blood cells, 20,500; polymorphonuclears, 82 per cent; lymphocytes, 10 per cent; monocytes, 6 per cent; eosinophiles, 2 per cent.

The child died one day after admission.

*Autopsy Findings.*—Bronchopneumonia of right lower lobe. Marked cerebral edema and hydrocephalus. Large hemorrhagic infiltrating tumor of left frontal lobe involving corpus callosum and a portion of the fornix and internal capsule.

*Histologic Diagnosis.*—Medulloblastoma cerebri.

CASE 5.†—T. H., aged four years, white. Four days before admission the patient had a headache and began to vomit twice daily. There was pain on urination for one day.

*Physical Examination on Admission.*—The child, poorly nourished, was drowsy and complained of pain on flexing the neck. There were slow sighing respirations and frequent extrasystoles. Slight tenderness and a walnut-sized mass, hard and movable, in the midline of abdomen below umbilicus were noted. The blood sugar level was 89; blood urea nitrogen, 11; carbon dioxide combining power, 41.

The child died one day after admission.

*Autopsy Findings.*—The lymphoid structures throughout the body were hypertrophied. A large cystic tumor of the left cerebellar hemisphere was found causing pressure on the medulla and the fourth ventricle.

*Histologic Diagnosis.*—Medulloblastoma cerebelli.

CASE 6.‡—P. T., aged eleven years, white. Eight months previously the patient had a tonsillectomy and two weeks later had an attack of headache and vomiting. These attacks recurred weekly until admission and were accompanied by increasing weakness and loss of weight.

*Service of Dr. Le Boutillier.
†Service of Dr. W. N. Bradley.
‡Service of Dr. M. P. Warmuth.

*Physical Examination on Admission.*—Mental development was normal. There was dysarthria, and the head was comparatively large. Nystagmus in all directions, mostly to the right, was present; the left pupil was larger than the right. Optic disks were blurred, more on the right than the left. There was inconstant weakness of the lateral rectus muscle of both eyes. The tongue deviated slightly to right and showed slight atrophy of the right side with fibrillar tremors. The child tended to fall to the left and could not stand alone. The gait was ataxic and the muscle tonicity, poor. There was marked ataxia of both upper and lower extremities. There was past-pointing to the right. The blood pressure was 190/60. Spinal fluid pressure was 40 mm. of mercury. The spinal cholesterol and Noguchi antigen agglutinations were negative. The red blood cell count was 5,300,000; hemoglobin, 13.8 gm.; white blood cells, 9,400; polymorphonuclears, 73 per cent; lymphocytes, 26 per cent; eosinophiles, 1 per cent.

The blood sugar level was 100 and blood urea nitrogen, 12.

The roentgenogram of the skull showed sutures wider than normal and signs of increased intracranial pressure. Eleven days after entrance to the hospital craniotomy was performed, and a large cyst of the cerebellar type was found.

Fig. 3.—Case 6. Astrocytoma. Right lower longitudinal quarter-section of brain showing large cystic tumor arising from the right cerebellar hemisphere and encroaching upon the medulla and all the lower cranial nerves.

The patient died a few hours later.

*Autopsy Findings.*—The brain was one and one-half times normal size. There was marked edema and internal hydrocephalus. A large cystic tumor was found arising in right cerebellar hemisphere and encroaching upon the medulla, cerebellopontine angle, restiform body, and all the cranial nerves on the right below the eighth.

*Histologic Diagnosis.*—Astrocytoma.

CASE 7.*—J. McH., aged eight years, white, suffered from vomiting and left frontal pain for three weeks before admission (Nov. 13, 1935). Drowsiness followed the vomiting attacks. There was a weight loss of 10 pounds.

*Physical Examination on Admission.*—The margins of the optic disks were blurred. The blood pressure was 92/65.

*Laboratory Findings.*—Spinal fluid—pressure, 8 mm. of mercury; Queckenstedt test, questionably positive on left after removing fluid; 4 cells; trace of globulin; sugar, 70; chlorides, 732; culture, negative; cholesterol antigen agglutination, negative; colloidal gold curve, 222332100. The differential blood count showed red blood

*Service of Dr. Le Boutillier.

cells, 4,090,000; hemoglobin, 12 gm.; white blood cells, 5,600; polymorphonuclears, 70 per cent; lymphocytes, 26 per cent; mononuclears, 2 per cent; eosinophiles, 2 per cent.

On November 18 the spinal fluid pressure was 8 mm. The right pupil was slightly larger, and horizontal nystagmus to both sides and slightly vertically was noted. The left eyelid dropped slightly, and both optic disk margins were blurred. There were slight right facial weakness and slight dimness of vision in the left eye. Positive Babinski and Oppenheim reflexes were elicited on the right. On November 20 the patient was more drowsy and irritable. The spinal fluid pressure was 24 mm.; blood sugar, 77; urea nitrogen, 9; Kahn test, negative.

An x-ray film of the skull showed convolutional atrophy indicating increased intracranial pressure. On November 24 projectile vomiting, severe headache, and slowing of cerebration were noted. The disks were choked ½ D, right eye, and 1 D, left eye; the veins were dilated, and a small hemorrhage was present on the left. On November 26 cerebellar asynergia on the left side, adiadokokinesis in left

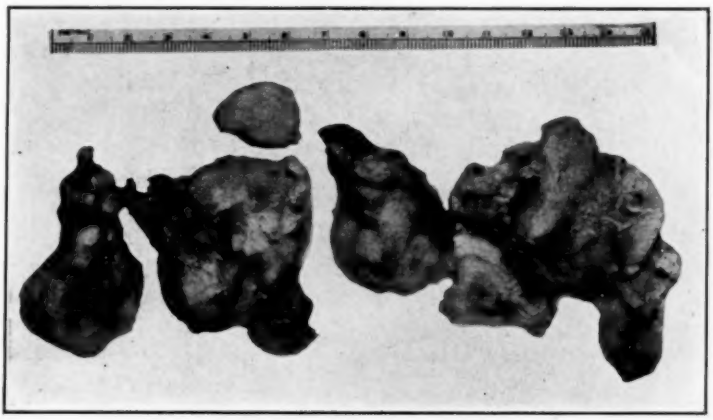

Fig. 4.—Case 7. Unclassifiable pleomorphic neurogenic tumor, embryonic in type. Specimens are pieces of tumor removed from left temporal lobe at operation.

arm, and slight deviation to the right in walking were present. At this time a diagnosis of medulloblastoma of the cerebellum in midline with extension to the left was made. The patient was placed on a dry diet with limited fluids, and deep x-ray therapy was begun. On this regime at first the symptoms became exaggerated with choking of disks increasing to 5 D bilaterally; improvement and complete disappearance of symptoms and choking followed. On Jan. 5, 1936, the patient was discharged.

On January 13 the child was readmitted after the return of the headache and vomiting at home. Choking of the disks had returned, and facial weakness on right was more marked with complete paralysis of the third nerve on the left. X-ray therapy was resumed.

On January 28 sudden increase in intracranial pressure caused unconsciousness and beginning respiratory failure. Responded well to dehydrating enema and IV glucose.

On January 29 a suboccipital craniectomy was done by Dr. F. C. Grant, who found no tumor.

On February 5 a ventriculogram was made, and viscid yellow fluid was aspirated from left cerebral hemisphere near the lateral ventricle. After injection of air, the x-ray film showed a cyst in the left temporal lobe.

On February 26, after several transfusions in preparation for the operative procedure, Dr. Grant made a left temporoparietal bone flap and removed a large tumor and cyst from left temporal lobe.

The child's course since operation has been downhill, with loss of weight, early optic atrophy, and a wound infection with osteomyelitis of the bone flap, which had to be removed May 27. Another operation was performed on June 20, and several large masses of tumor were removed from site of previous operations.

*Histologic Diagnosis.*—Pleomorphic neurogenic tumor, embryonic in type and not classifiable according to tables of Cushing and Bailey.

CASE 8.*—W. K., aged five years, white, had a cold in November, 1931, followed by cough in December. The mother noticed enlargement of the inguinal glands. There were gradually increasing weakness, loss of weight, and moderate night sweats.

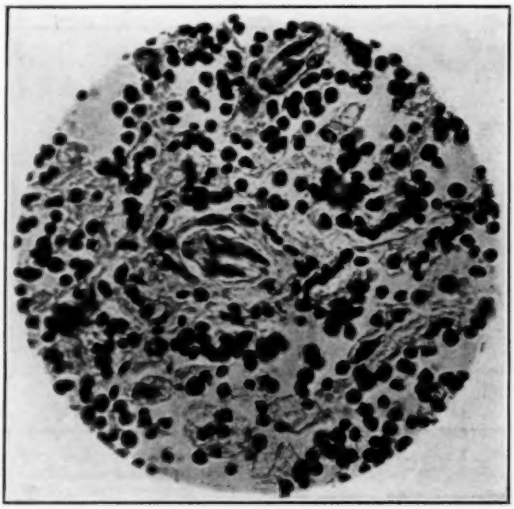

Fig. 5.—Case 8. Metastatic lymphocytoma nodules on subdural surface of middle fossa. Note perivascular distribution of the large metastatic cells from the primary thymic lymphocytoma.

On admission in June, 1932, the child was undernourished. There was frontal bossing and palpable cervical nodes.

The inguinal nodes were large and adherent to each other. The heart was displaced to right, but the lungs were clear. The blood Kahn test was negative.

Gradually the child became more dyspneic, then developed nuchal rigidity and opisthotonus, and died ten days after admission.

*Autopsy Findings.*—Thymic tumor, primary lymphocytoma. The heart showed epicardial hemorrhage and hydropericardium. Findings in the left lung included atelectasis of the upper lobe, emphysema and bifid lower lobe, and subpleural petechiae. The right lung showed acute congestion and edema. Bilateral hydrothorax was present. Spleen, kidneys and lymph nodes showed secondary lymphocytomas.

*Service of Dr. W. N. Bradley.

In the brain were numerous elevated, hemorrhagic, irregular areas on subdural surface of middle fossa close to vertex.

*Histologic Diagnosis.*—Metastatic lymphocytoma from thymus.

CASE 9.*—M. T., aged six years, white. The mother noticed that the patient was weak and drowsy and had lost his appetite two months before admission. Improvement followed the use of a tonic, until two weeks before admission to the hospital, when vomiting accompanied by lethargy was noted. These symptoms persisted.

*Physical Examination on Admission.*—The child was emaciated and semistuporous. The following findings were noted: frontal bossing, ptosis of left eyelid, weakness of the left external rectus muscle, and right homonomous hemianopsia. The eyegrounds showed pallor in the temporal half of the left disk and the right disk choked 1 D. There were slight right facial weakness, marked nuchal rigidity, and

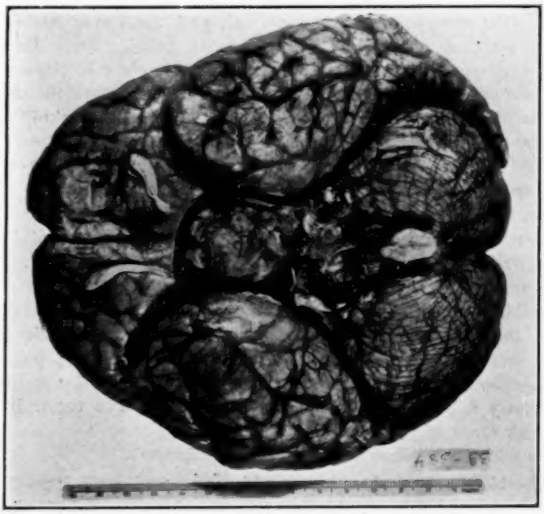

Fig. 6.—Case 9. Swannoma, a firm encapsulated tumor arising from the optic chiasm and filling the interpeduncular space. Also fusiform neurofibromas on left median and both ulnar nerves and along the brachial plexus.

palpable cervical nodes. The respirations were slow and deep, and there were diffuse abdominal tenderness and general hyperesthesia. *Tache cérébrale* was present. There were bilateral positive Kernig and Brudzinski signs and a bilateral Babinski reaction. Slight ataxia in the right arm and both legs, marked weakness and atrophy of the musculature, and diffuse light brown pigmentation of the skin in large macules were noted. On the palmar aspect of the right forearm was a discretely movable, nontender nodule. The blood pressure was 136/116.

Spinal fluid findings were as follows: pressure, 30 mm. of mercury; 3 cells per cubic millimeter; sugar, 78; chlorides, 726; test for tubercle bacilli, negative; Levinson and tryptophane tests, positive. Red blood cells numbered 2,450,000 with hemoglobin, 50 per cent; white blood cells, 5,200; polymorphonuclears, 60 per cent; lymphocytes, 34 per cent; and monocytes, 6 per cent. Blood sugar level was 100, urea nitrogen, 9.

*Service of Dr. T. Fay.

X-ray film of skull was negative. Biopsy of nodule in forearm showed a neurofibroma. The pulse and respirations remained slow, the lowest rates being 60 and 6, respectively. Choking of the optic disks became more marked. Right ventricular tap was followed by no improvement. The patient died three weeks after admission.

*Autopsy Findings.*—In the lungs were found static infarcts and bronchopneumonia. A fusiform tumor of the left median nerve along the brachial plexus and ulnar nerves was also found. The sella turcica was increased in its anteroposterior diameter. The greatest erosion was in the anterior clinoids, especially the left. The diaphragm of the sella was intact. The pituitary was small and atrophic. The optic nerves as they enter the optic foramen were larger than normal but did not show any tumor formation. The brain was enlarged as a result of an enormous obstructive hydrocephalus. The pia-arachnoid was dull and hazy, and there were milky plaques over the tips of the temporal lobes and along the sylvian fissures. In the interpeduncular space there was a firm tumor, lobulated with some cystic areas. The tumor measured 3 by 4 cm.

The optic chiasm was larger than normal, and the tumor was intimately attached to its posterior border. It appeared to be growing from the chiasm. The tumor was encapsulated and at no point was attached to the hemisphere. It sprang up between the peduncles and between the temporal lobes filling the interpeduncular space, but involved these areas only by pressure. It pressed back against the basis pontis. There was no attachment to any of the cranial nerves except the optic chiasm. The left third cranial nerve was small as if involved by pressure.

The basilar artery gave off the posterior cerebral arteries at the posterior limit of the tumor, and the posterior communicating arteries were stretched to thin hairs along the lateral boundaries of the tumor mass. The internal carotid arteries were pushed laterally by the tumor.

On anteroposterior section it was seen that the tumor extended up into the cerebrum through the third ventricle. It had filled the body of the lateral ventricles but had not invaded the brain structure except by pressure. The capsule of the tumor separated it from the thalami. It had blocked off the anterior, posterior, and inferior horns. The anterior were greatly dilated, and the posterior and inferior horns had formed only a large cavity in either hemisphere. The tumor itself was firm and fleshy with areas of yellow necrosis.

*Histologic Diagnosis.*—Swannoma (central neurinoma).

CASE 10.*—M. K., aged three years, white, was well until June 30, 1935, when he became irritable and drowsy. On July 2 he complained of pain in the epigastrium. The next day walking was difficult, as though "there were nails in his shoes sticking his heels." On July 4 he was irritable but could walk. On July 8 there were anorexia, vomiting after an enema, headache, and drowsiness. On July 9 the child, unable to walk, became drowsy and was taken to a hospital where a diagnosis of anterior poliomyelitis was made; the patient was transferred to the Philadelphia Hospital for Contagious Diseases. On admission there he was drowsy and irritable. Examination showed a positive Brudzinski sign, absent abdominal reflexes, flaccid paralysis of both lower extremities with absent deep reflexes, no Babinski or Kernig sign, or clonus.

In the spinal fluid there were found 38 cells per cubic millimeter. Polymorphonuclears were 80 per cent; lymphocytes, 20 per cent; sugar, 63.5; chlorides, 680; albumin, 2-plus; globulin, 1-plus; Wassermann test, negative; Levinson test, negative; smear, negative; culture, *Staphylococcus albus* (contamination?).

Low fever persisted for the first five days; temperature was normal for ten days; then there was a moderate fever (highest 103° F. rectal) for one week. The patient developed loss of pain and temperature sensations up to the costal margin.

*Service of Dr. W. N. Bradley.

Later lumbar and cisternal taps gave positive Queckenstedt reactions, and the fluid showed the Froin-Nonne phenomenon. X-ray films of the cervical and the thoracic vertebrae were negative. There was slight return of motion in the toes and the feet.

On August 16, after transfer to the Philadelphia General Hospital, he was drowsy and irritable. Nuchal rigidity with a positive spine sign was present. Cremasteric and abdominal reflexes were absent. The rectal sphincter was relaxed. There was flaccid paralysis of the lower extremities. The child was able to move his feet and flex his legs on painful stimuli, but apparently he did not feel pain there. The pain and temperature senses were absent up to costal margin. The tendo achillis reflexes were present but weak. On August 20 a neurologic consultant confirmed the above findings and also found a bilaterally positive Babinski reflex. The spinal fluid was bloody, with a pressure of 6 mm. of mercury and a positive Queckenstedt sign. On August 21 the spinal tap was again bloody; cisternal tap gave clear fluid, under a pressure of 12 mm., trace of globulin, and a negative Queckenstedt sign. On August 23 the x-ray films of the vertebrae were negative. Red blood cells numbered 4,780,000, with hemoglobin, 14 gm.; white blood cells, 12,000; polymorphonuclears, 74 per cent; lymphocytes, 12 per cent; and monocytes, 14 per cent.

On August 28 lipiodol injected intracisternally and x-ray showed definite complete obstruction at the fifth thoracic vertebra. Laminectomy performed at the sixth thoracic vertebra by Dr. Duane revealed a fusiform swelling of the cord; the dura was not involved; a hemorrhagic infiltrating tumor of the cord itself was found.

Biopsy showed a sympathicoblastoma.

Deep x-ray therapy was begun, and two courses totaling 3,500 r. units were given over the location of the tumor.

On September 2 wound infection was noted.

On September 6 x-ray film of abdomen showed no mass or calcification.

On October 5 x-ray examination of skull and long bones showed no metastatic lesions; there were increased bony trabeculations, decalcification, rarefaction of centers of ossification, thickened cortex, and periostitis on tibial borders.

On October 15 the child was irritable, with twitching of facial muscles and rolling of eyes. The blood Kahn test was negative; blood serum calcium, 10.9; phosphorus, 5.4.

On November 13 he was irritable. Twitching of right forearm was noted. Respirations were irregular; neck, stiff; Babinski sign, still positive bilaterally.

On December 23 he was apathetic. Respirations were labored, and he was slightly cyanotic. Ptosis of right eyelid, right facial weakness, and irregular rolling of eyes were noted.

On December 24 the child died.

*Autopsy Findings.*—Adrenals showed no evidence of tumor. There was no involvement of the skull.

There was smoothing out of convolutional markings, and the brain appeared tense. The ventricles were dilated. At the base there was a tumor mass compressing the left side of the pons and medulla. This was encapsulated, soft, white, with areas of hemorrhage into it. It measured 3 by 2 by 2 cm. It involved the brain only by pressure, pressing upon the left middle cerebral peduncle, the restiform body, the inferior olive, and the nerves emerging at these levels. The cranial nerves appeared to be intimately involved in the capsule of the tumor, which was very thin. Small tumors were attached apparently to the sheath of the twelfth cranial nerve on the left, and the ninth and tenth cranial nerves on the right, and one was noted springing from the sheath of the right third cranial nerve. These tumors were less than 0.1 cm. in diameter and were very closely connected with the

nerves. Because of pressure against the pituitary fossa, there was a deep groove just anterior to the optic chiasm, which appeared to cause compression of the anterior cerebral vessels.

Fig. 7.—Case 10. Neurogenic tumor composed of embryonic differentiating cells. Large, soft, white but hemorrhagic tumor mass pressing on the left side of pons and medulla. Several small tumor nodules arising from the sheaths of lower cranial nerves.

Fig. 8.—Case 10. Neurogenic tumor composed of embryonic differentiating cells. Sections through cervical and thoracic levels of spinal cord showing intramedullary and extramedullary involvement with firm hemorrhagic tumor.

There was no involvement of the spinal canal. The dura was tense, and the cord filled it tightly. Upon section at the level of the old laminectomy (sixth thoracic)

the entire cord was found to be replaced by firm white cartilaginous tumor. Just above this level the cord was crowded to one side by a large mass of tumor. This tumor may have been within the pia-arachnoid, but it did not appear at first to be intramedullary. The first two thoracic segments and the cervical segments presented a long tongue of hemorrhagic material surrounding the posterior and lateral surfaces. This was too firm for hemorrhage alone and suggested hemorrhagic tumor. Below the level of the sixth thoracic segment no tumor was noted grossly.

*Histologic Diagnosis.*—As in Cushing's case the tumor tissue removed at autopsy showed a greater differentiation in cell type than did the original biopsy. Neurogenic tumor composed of embryonic differentiating cells is the best diagnosis of this tumor.

Neurogenic tumors arising from the sympathetic nervous system in children are fairly common, the sympathicoblastomas originating in the adrenals being the most frequent type, many cases of which have been reported in the literature. The more rare locations reported are the cervical region, sphenomaxillary region, thorax, dorsal sympathetic ganglion, stomach, abdomen, liver, intestine, uterus, pelvis, perineum, skin of thigh, and vagina; one author cites a case with multiple foci of origin. However, in all the literature there was no instance of such a tumor type arising from the spinal cord itself as in the case reported here.

## DISCUSSION

In spite of the occurrence of the various signs and symptoms summarized above, which were suggestive of the diagnosis of brain tumor in this group of patients, it is well to note the difficulties in making such a diagnosis in certain instances.

In Cases 1 and 2 there were few definitely abnormal neurologic findings on admission, and yet at autopsy, performed one day and two weeks later, respectively, the tumors were large space-taking lesions.

Cases 2 and 5 also show that the size of the lesion is not necessarily commensurate with the duration of the symptoms. Compensating variations in blood flow and cerebrospinal fluid circulation may take care of the gradually increasing size of the tumor mass, and the new-growth often attains a large size and replaces a great deal of cerebral tissue before cerebral decompensation takes place. Then the signs and symptoms of increased intracranial pressure become manifest. In Case 2 the child had symptoms but one day before coming to the hospital; yet fifteen days later at operation the tumor had replaced most of the left frontal lobe. In Case 5, with headache and vomiting of four days' duration, there was a large cystic tumor of the cerebellum at autopsy performed five days after the onset of the illness.

One of the greatest lessons to be learned from this series of brain tumors becomes apparent when the diagnoses made by the physicians sending these patients to the hospital for study are listed:

| | |
|---|---|
| Brain tumor | 2 |
| Pulmonary tuberculosis with tuberculous meningitis | 2 |
| Fractured skull | 1 |

| | |
|---|---|
| Hydrocephalus | 1 |
| Meningitis | 1 |
| Poliomyelitis | 1 |
| Uremia | 1 |
| Gastroenteritis | 1 |

Both physician and parents are too prone to dismiss the symptoms which usually precede the physical signs, as being due to some irrelevant occurrence in the past history. This *post ergo propter* logic was applied in Case 4 in which a slight head injury was indicted merely because it preceded the symptoms. What child is there, whose parents cannot remember a head trauma of slight degree in the past? However, it must be kept in mind that head trauma may cause hemorrhage into a preexisting tumor and thus exaggerate the symptoms as in Case 2. Because the patient in Case 3 had a severe attack of pertussis prior to the onset of deafness and later blindness, the blame was placed on the pertussis. A tonsillectomy was taken to be the cause of the symptoms in Case 6 merely because it had been done two weeks before their onset; an indefinite idea of a birth injury or some congenital neurologic disease was the explanation in Case 1.

## SUMMARY AND CONCLUSIONS

Case histories and either autopsy or operative findings of ten cases of brain tumor in children have been presented. The features in each case which were responsible for the diagnosis' being made late in the disease have been pointed out, and a summary of the symptoms and physical and laboratory findings in this series is given for the purpose of emphasizing the importance of considering brain tumors under certain circumstances in pediatric practice.

It is easy to point out the mistakes of the general practitioner after the diagnosis is established, but this has been done only to recall the fact that the diagnosis of brain tumor should suggest itself whenever a child has a headache and vomiting with no apparent cause for more than a few days or whenever any abnormal neurologic finding presents itself. This series of cases also brings out the importance of eyeground examinations in suspicious cases and the necessity of a pediatrician's knowing how to use the ophthalmoscope correctly.

I am indebted to Dr. Helena Riggs for the neuropathologic descriptions and diagnoses in this paper.

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# IV. THE TREATMENT WITH GONADOTROPIC HORMONE (ANTERIOR PITUITARY-LIKE) OF NONADIPOSE BOYS SHOWING GENITAL DYSTROPHY

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ON PERUSING the literature that has accumulated during the last few years on the nonoperative treatment of imperfectly developed testicles and genitals, I found that almost all the cases reported which responded to treatment, particularly to treatment with anterior pituitary-like hormone, were those with adiposogenital dystrophy.[1-8] While it seems true that cases of adiposogenital dystrophy are seen more often, cases of genital dystrophy without obesity are also encountered and should not be overlooked. To date, however, very little has been reported on the effects of hormone treatment on genital dystrophy in the nonadipose boy. The effects on the genitals in the few nonadipose cases that I found reported varied. Several showed response to gonadal stimulation,[2, 4, 10] while others showed no response.[3, 9] Since I have had occasion to see and to treat some nonobese boys who had genital dystrophy, I believe that the following report is timely.

I believe there is the possibility that the cases of the nonobese boys reported in the literature, or those encountered and not reported, might have failed to respond to hormonal therapy, not because the nonadipose boy could not respond to such therapy, but rather because there were certain factors which determine the outcome of hormonal treatment for genital dystrophy which should have been taken into consideration. From personal experience, I have found that certain factors for the adipose boy should be applied to the nonadipose boy, namely,

1. A diagnosis must be made to determine the primary offending gland before corresponding hormonal therapy can be instituted rationally.

2. The onset of treatment must be instituted before puberty, when receptor tissues are responsive; postpubertal treatment often finds unresponsive tissues.

3. A potent product must be used, and the dosage and frequency of injection must be regulated judiciously.

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Presented at the New York Endocrinological Society on March 24, 1937.

4. Sufficient therapy must be given over a sufficiently long period of time before a complete result can be attained.

5. If, after proper therapy has been administered judiciously over a period of time, there is no testicular descent, hormonal therapy may be considered inefficacious and the existence of mechanical obstruction for the nondescent may be considered. Anorchidism is a rarity.[10]

One might question the basis upon which the same factors mentioned above for the obese boy with genital dystrophy could have been applied to the nonobese boy with a similar genital condition. This has been done with the belief that the obesity in these cases was not directly related to the hypogonadism. As a matter of fact, I have found and previously reported,[7] as have others,[1] that after treatment of the gonads with anterior pituitary-like hormone from the urine of pregnant women existing obesity was not corrected by such hormonal therapy even though the gonads were made to respond completely. In fact, the opposite was often true: weight during treatment with this hormone was increased, and the increment was found to be greater than that prior to treatment.[7]

I believe that both types, the nonadipose boys with genital dystrophy as well as the adiposogenital dystrophic boys, with very few exceptions, should be considered from an endocrinologic standpoint, for obesity in itself is not the factor determining whether a case is of endocrine or nonendocrine origin. Rather, there are other more definite criteria which do point to the nature of the case and to the possible endocrinologic dysfunction. These must be considered in the diagnosis, in order to determine what gland is primarily involved in causing the disturbance. Briefly they are as follows:

In addition to genital dystrophy, if there are:

1. Accelerated height and eunuchoid characteristics, these disturbances indicate a primary hypogonadism.

2. Dwarfism, leanness, these disturbances point to a possible primary hypopituitarism, although a diagnosis of the aneoplastic type is difficult to establish clinically because of the present lack of conclusive diagnostic criteria.

3. Mental, physical, somatic, or osseous retardation, such as stunted stature, poor mental responses, sluggishness, delay in the appearance of ossification centers and delay in closure of the epiphyses, or low basal metabolism; such disturbances indicate a primary hypothyroidism. (I have reported previously cases of this type, with some of such deficiencies, in "Masked Hypothyroidism in Children."[11])

The above are all-important diagnostically as aids in determining the therapy necessary for securing completely successful results. For,

while it is true that gonadal and genital correction usually can be achieved simply through the administration and prolonged use of anterior pituitary-like hormone in most of the cases, some of the other disturbances of a mental, physical, somatic, or osseous nature, usually accompanying the genital dystrophy, cannot be corrected by simple gonadal treatment alone. Therefore, in addition to having to correct the genital dystrophy with gonadal therapy, very often these other deficiencies must also be treated before one can get a complete result and be justified in considering the case entirely corrected.[8]

With the above points in mind, I am reporting the cases of two boys with genital dystrophy without obesity, who showed various other deficiencies associated with endocrine unbalance. I am including, too, some mention of the treatment with various hormonal substances and of the responses evoked. I hope that all this will prove an aid both diagnostically and therapeutically and that in addition it will serve as a contribution to the meager literature on such types of cases.

CASE 24.—T. F., aged seven and one-half years, was referred to the endocrine clinic on April 8, 1935, because of backwardness in school. He had been left back in his first class for three terms. The infantile history was normal except for the onset of walking at eighteen months and the onset of talking at thirty months. Examination of the patient showed the following pertinent observations:

His skin was dry; his hair was coarse and sparse. His features were somewhat cretinoid. His mouth gaped, and there was a tendency for his tongue to protrude. He had many carious teeth. He was sluggish and retarded mentally. His weight was 57¾ pounds (average normal for age, 45 to 55.8 pounds), and his height was 47¾ inches (average normal for age, from 46.6 to 49.8 inches). The upper trunk was in normal relation to the lower extremities.

On examination of the genitals, it was found that a pea-sized left testis could be pushed down very easily into the scrotum, but then it returned with the same ease to its original position in the canal. The right testis was even slightly smaller and was situated high up in the canal; it could not be pulled down into the scrotum. There was a thickened processus extending from the proximal pole of the right testicle. The right portion of the scrotal pouch was not formed. The penis measured about 1⅛ inches. Enuresis was present.

Roentgenograms of the head showed no cranial or intracranial pathology. The sella turcica was somewhat smaller than the average for the size of the skull. The osseous development showed a bone age equivalent to four and one-half years—a retardation of about two and one-half to three years as compared with the patient's chronologic age.

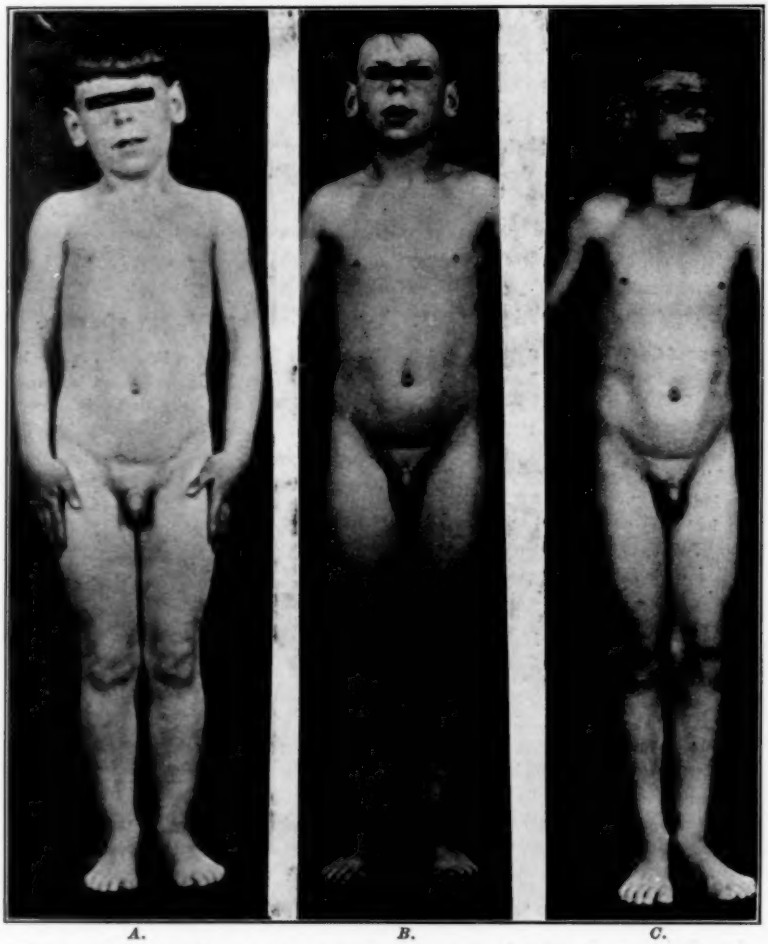
The laboratory data were as follows: A fasting blood chemistry examination showed cholesterol, 100 mg.; nonprotein nitrogen, 22; creatinine, 2; uric acid, 3.6; sugar, 80; calcium, 6.5; and phosphorus, 4.5. Urine specimens taken before and during treatment were normal.

The patient could not cooperate for a basal metabolic test.

The diagnosis of this case was hypothyroidism with secondary genital dystrophy.

After this first examination in April, 1935, the patient was given desiccated thyroid for a number of weeks. A definite general improvement ensued. However, there followed no gross apparent genital improvement in this short period. Thyroid was then discontinued.

On Nov. 30, 1935, when he was eight years old, after thyroid medication had been discontinued for some time, the patient's height was 48 inches (average normal for age, from 47.5 to 50.9 inches) and his weight was 60.25 pounds (average normal for age, from 47.2 to 58.4 pounds). At this time intramuscular injections of anterior pituitary-like hormone derived from the placenta,* in doses of 100 and



*A.* *B.* *C.*

Fig. 1.—*A*, T. F. (Case 24), aged seven years six months, before treatment with gonadotropic hormone (May, 1935).

*B*, T. F. after four months of treatment with anterior pituitary-like hormone of placenta (10,000 biologic day units) (March 23, 1936). Note no change in genitals.

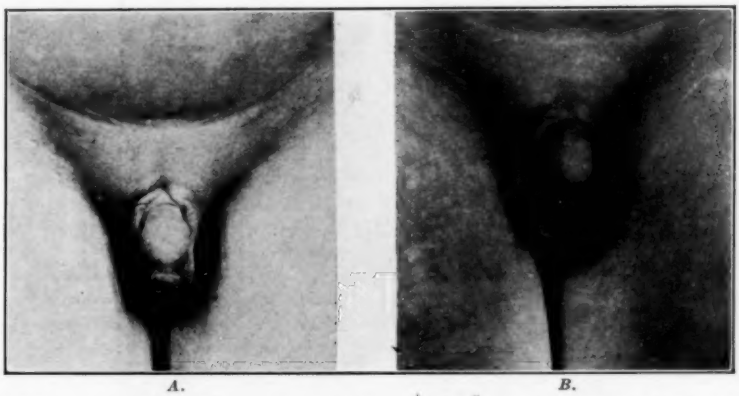
*C*, T. F. in September, 1936, after three months of treatment with anterior pituitary-like hormone of pregnancy urine (39,000 R. U.). Note the definite advance in the development of the genitals.

*Anterior pituitary-like hormone is standardized in terms of Collip rat units. One unit is that quantity of anterior pituitary-like hormone which, when administered by subcutaneous injections daily, for three successive days, into twenty-one-day-old female albino rats weighing 28 to 40 gm., will produce vaginal estrus within 120 hours in 50 per cent of a group of ten rats thus injected.

then 200 units, were given three times a week. During a period of seven months the patient received a total of 120 c.c. of anterior pituitary-like hormone totaling 12,000 units. In spite of this, the gonadal stimulation after this course of treatment with the placental hormone was nil; only when pituitary hormone "maturity factors"* was given along with it for a short time (1 c.c. per dose, 17 c.c. in all) did there appear evidence suggestive of some gonadal stimulation.

In view of this complete lack of response with the placental hormone, and the very small response with the maturity factors, anterior pituitary-like hormone derived from pregnancy urine† was then substituted (May 25, 1936) in doses varying from 500 to 1,200 rat units per injection, the usual dose being 1,000 units, three times per week.

After one month of this treatment (the patient now having received 11,000 rat units of anterior pituitary-like hormone from pregnancy urine), it was noted that for the first time the right testicle was now resident in the scrotum and was about the same size as the left testicle. The skin of the penis and of the scrotum was definitely reddening, and the right portion of the latter was filled out. The enuresis apparently was being controlled.



*A.* *B.*

Fig. 2.—*A*, genitals of T. F. (Case 24) on March 23, 1936, after treatment with 10,000 biologic day units of anterior pituitary-like hormone of placenta. Note the lack of development of right portion of scrotum and absence of right testicle from scrotum. Compare and note similarity of genitals as in Fig. 1, *A* and *B*.

*B*, same patient six months later (Sept. 1, 1936) after four months of treatment with 39,000 rat units of anterior pituitary-like hormone of pregnancy urine. Note the right testis in midscrotum and the formation of the right portion of the scrotum.

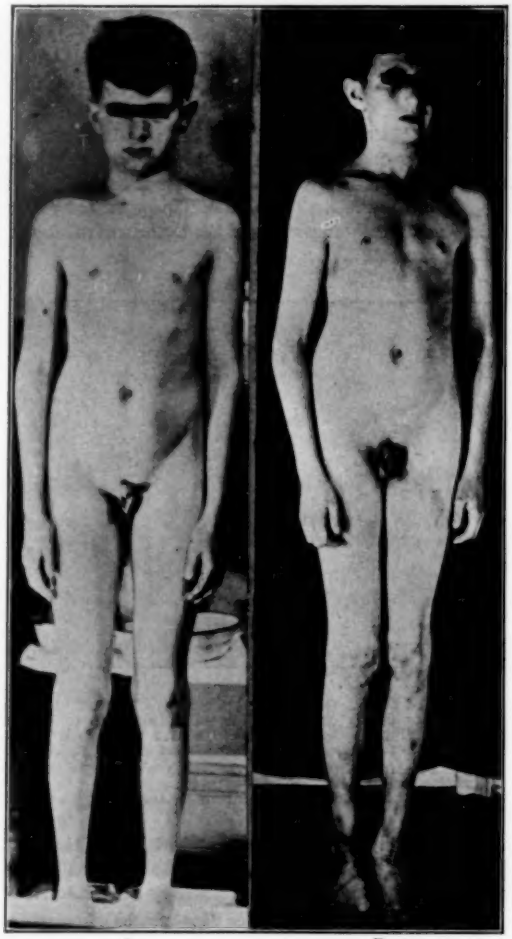
During the ensuing six weeks, the patient received an additional 14,000 rat units, the aggregate now totaling 25,000 rat units of the hormone of pregnancy urine. After this treatment the genital response seemed very satisfactory.

At the present time (October, 1936), after four months of treatment with anterior pituitary-like hormone from pregnancy urine, an aggregate of 39,000 R.U., the patient is showing progressive improvement of the genitals. In addition, his height

*"Maturity factors" is a gonadotropic factor extracted from the anterior pituitary gland. It contains also small amounts of other hypophyseal factors. The potency of this product was 25 units per cubic centimeter. One unit is one-tenth of that amount which, when administered daily, in three divided doses, for three days, to a group of at least ten twenty-one-day-old rats, each weighing between 30 and 40 gm., produces ovaries having a combined weight of 40 to 50 mg. seventy-two hours after the first injection.

†The maturity factors, and the placental and pregnancy urine hormones were supplied through the kindness of Mr. Robert E. Sachs, of Ayerst, McKenna & Harrison, Montreal, Canada.

is now 49⅞ inches, an increase of 2 inches, and his weight is 66 pounds, a gain of 8¼ pounds in seventeen months. His bone development is now equivalent to about the six and one-half year level; although there was some progress, there is still a bone lag of about two and one-half years. Further treatment is still being continued to assure fixation of the testicles in the scrotum and to accomplish a com-



*A.* *B.*

Fig. 3.—*A*, H. M. (Case 25), aged eleven years six months, before treatment (March, 1936).

*B*, H. M., after four months of treatment with anterior pituitary-like hormone of pregnancy urine (October, 1936).

plete gonadal response. Since, however, the other deficiencies, such as the mental and osseous retardation, were not completely corrected with the above gonadal treatment, thyroid medication has been resumed in addition to the gonadotropic hormone in order to correct such retardation.

CASE 25.—H. M., aged eleven and one-half years, was referred to the endocrine clinic because of malnutrition and lack of physical and genital development. (His younger brother also has genital underdevelopment.) The patient's infantile developmental history was apparently normal.

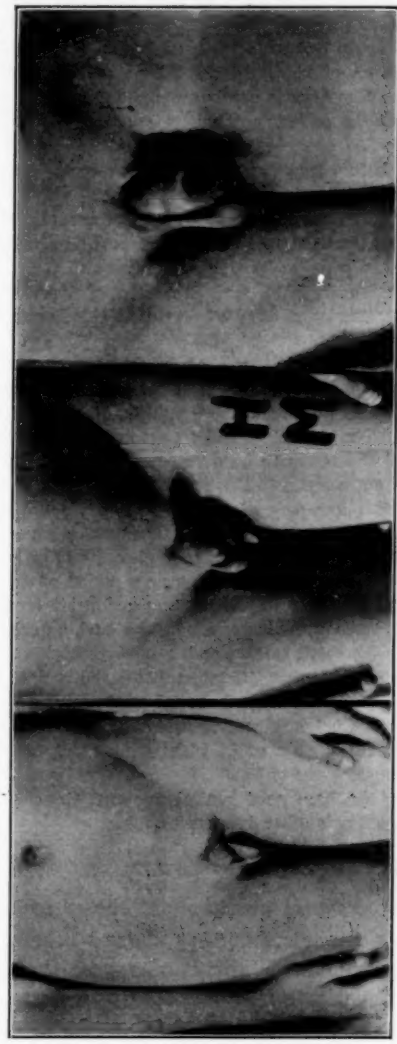



FIG. 4.—*A*, genitals of H. M. (Case 25) before treatment (March, 1936). *B*, genitals of H. M. after treatment with 11,000 R. U. of anterior pituitary-like hormone of pregnancy urine given over a period of four weeks (August, 1936). Note the descent of the testes and enlargement of the scrotum and penis. *C*, genitals after 36,000 R. U. of anterior pituitary-like hormone of pregnancy urine given over a period of four months (October, 1936). Note the residence of the testicles in the scrotum and enlargement of scrotum and penis.

Examination of the patient in February, 1936, showed a slim, frail, and somewhat short individual. There was no myxedema. His height was 54.75 inches (the average normal for age being from 54.3 to 58.1 inches); his weight was 62 pounds (the average normal for age being from 66.2 to 83.2 pounds). The relationship

between his upper and lower measurements was eunuchoid. He was mentally alert. There was a soft systolic murmur present at the apex. Moderate pes planis was present.

An examination of the genitals showed the left testicle to be fixed at the internal ring. The right testicle was more definite to touch and was situated in the canal, but it could not be pushed into the scrotum. The penis measured about 1¼ inches in a semi-erect state, and it was retracted somewhat in a labia-like fold of the scrotum. Enuresis was not a factor in this case.

A roentgenologic examination of the head showed no pathology of the skull; the sella turcica was normal. The osseous development showed a bone age of about eight years as compared with the patient's chronologic age of eleven and one-half years.

The basal metabolic rate before treatment was -20.4 per cent; later, during the treatment, it was -17.2 per cent.

A diagnosis of hypothyroidism with secondary genital dystrophy was made although superficially the patient seemed to resemble the Levi-Lorain type of hypopituitarism.

Treatment was started in March, 1936, with injections of "maturity factors" from 1 to 2 c.c. three times a week. A total of 48 c.c. of this hormone was given over a period of two months.

At the end of this time there was evidence of definite but slight improvement in the genitals. There was some slight reddening of the sexual skin, and the testes, though still the size of a small pea, were now more mobile and could be pushed down to the neck of the scrotum. The patient missed treatment for one month. On his return reexamination showed the testes to have resumed their original position although they could be pushed down again to the neck of the scrotum.

At this time, in June, 1936, a supply of maturity factors not being available, treatment by injection with anterior pituitary-like hormone of pregnancy urine was instituted. From 500 to 1,000 rat units per dose were given by injection three times per week. A total of 18,000 rat units were given over a period of six weeks. The results were very gratifying. The skin of the scrotum and penis became markedly reddened; the scrotum and penis were increased in size and appeared more matured; and both testes were increased in size and became resident in the scrotum.

At the end of four months' treatment (October, 1936) the patient had received a total of 36,000 rat units of this hormone and showed a marked improvement in his genital system. In addition, his height since the first examination of eight months before, increased to 55½ inches, a gain of ¾ inch; his weight was 66¼ pounds, a gain of 4½ pounds for the same period.*

At this point, since there has been good genital response, thyroid therapy is to be instituted to correct the patient's other deficiencies.

## DISCUSSION AND COMMENT

It is important to note several points about the cases cited:

1. The patients were not obese, but they showed other evidence of definite endocrine disturbances. While it was true that out of my group of a few hundred patients with genital dystrophy, most of the boys showed obesity or adiposity in addition to other disturbances; nevertheless there were a number who were not obese but did show evidence of some of the same endocrinologic disturbances as the obese

*In March, 1937, one year since the first examination, the patient had gained 2¾ inches in height, and 13 pounds in weight. (Thyroid medication was not given as yet; anterior pituitary-like hormone was continued.)

boys. Obesity or nonobesity was not considered the factor determining whether the case was of endocrine etiology; all patients whether obese or nonobese were submitted to a complete endocrinologic study. As a result, it was usually found that, while a few showed no other stigma at the time except the genital dystrophy, nearly all of the nonobese boys, with very few exceptions, had endocrine disturbances of mental, physical, somatic or osseous nature in addition to genital dystrophy.

In previous reports I indicated that some of the endocrine disturbances (listed above) when accompanying a genital dystrophy could be associated with primary hypogonadism.[8] In the two cases just cited, I used the diagnostic criteria mentioned in this report for determining the offending gland responsible for the glandular dyscrasia, and I believe that the endocrine stigma accompanying the genital dystrophy was due, not to a primary hypogonadism as in the other cases, but rather to a primary hypothyroidism.[11] Histories of sluggishness, mental retardation, shortness in stature, and evidences of osseous delay were considered indicative of thyroid dysfunction in the present cases.

2. The gonads and external genitals of these thin boys could be made to respond favorably to treatment with anterior pituitary-like hormone. In these studies the anterior pituitary-like hormone extracted from the urine of pregnant women was found to be the most effective stimulant.

As to the effects of the other glandular therapy used, it can be said:

a. The pituitary factor or "maturity factors" of Collip seemed to produce some evidence of gonadotropic stimulation on the testicles; this agreed with the responses obtained by Werner and his coworkers[12] with another anterior pituitary gonadotropic hormone. Unfortunately, I was unable to carry my studies with this hormone far enough to enable a more detailed report at this time.

b. The anterior pituitary-like hormone extracted from the placenta was rather disappointing in its stimulative effects upon the gonads. My experience with this placental hormone, though limited, has shown that the stimulation which could be provoked on the gonads of the boy with genital dystrophy by anterior pituitary-like hormone from pregnancy urine could not be provoked by placental hormone. As a matter of fact, there seemed to be no apparent response whatsoever to the placental hormone.

Huddleston,[13] on the other hand, in a brief report on fifteen preadolescent boys with underdeveloped genitals, stated recently that the same effective response of the genitals produced by anterior pituitary-like hormone from pregnancy urine could be produced by the above mentioned placental hormone as extracted by the Collip method,

with doses as low as 100 units (from 50 to 100 rat units) administered daily for ten or fifteen days, and then 1 c.c. weekly for a time.

In contrast to Huddleston's findings, I not only got no results but I used as much as 200 units, three times a week for seven months, without producing any apparent gonadal stimulation whatsoever. I feel, though, that I cannot judge entirely from this because a larger series should have been studied and doses of higher concentration of this placental hormone tried. I intend to do this and make a study of the result at some future time.*

c. Desiccated thyroid (used in Case 24 and in other cases not reported here) was found to have stimulating effects, not only on the osseous and mental systems, but also on the gonads in cases of primary hypothyroidism. This thyroid stimulation of the gonads, however, was found to be very slow as compared with the stimulation with thyroid on other parts or as compared with the stimulation of the genitals by the anterior pituitary-like hormone of pregnancy urine. Therefore, the anterior pituitary-like hormone of pregnancy urine was used in cases of genital dystrophy for direct and rapid stimulation of the gonads; and in primary hypothyroidism in addition, desiccated thyroid was administered during the period of treatment when the hormone of pregnancy urine was administered, in order to provide stimulation to correct the other deficiencies.[8, 11]

3. It is true that anterior pituitary-like hormone therapy has been found to stimulate underdeveloped gonads, but since one usually finds more than a simple state of genital dystrophy—an additional state of physical, mental, and osseous retardation—other therapy, such as desiccated thyroid, as used in the two cases, should be supplemented to correct these other disturbances. I found that this other therapy, which I used in various other patients, has corrected most of such existing endocrine deficiencies due to primary hypothyroidism.[11] Desiccated thyroid, even for as short a period as a few weeks (Case 24) before anterior pituitary-like hormone of pregnancy urine was instituted, was seen to produce a definite general improvement.

## SUMMARY

1. The meager reports in the literature on the response to hormone therapy of preadolescent, nonadipose boys with genital dystrophy, has prompted the writer to report upon two such boys showing genital dystrophy without obesity, who were treated with hormone therapy, namely, anterior pituitary-like hormone of pregnancy urine.

*Personal communication to author by J. B. Collip, March 25, 1937.

"I am absolutely convinced that, whereas the placental hormone is separate and distinct from the pituitary gonadotropic substance, there is no essential difference between the physiologic effects of extracts containing the placental hormone irrespective of their source of origin, the possible sources being placental tissue, pregnancy blood or pregnancy urine . . ."

"Another important point is the A.P.L. unit.. My [Collip's] unit for this substance is probably considerably smaller than the unit used in certain commercial preparations, and I am firmly convinced that the differences which you noticed in the treatment of your cases can be explained entirely on the unitage used."

2. It is the opinion of the writer that the greater number of non-adipose boys with genital dystrophy, as well as adipose boys with genital dystrophy, usually show an endocrinologic basis for their genital disturbance. The writer has found from his experience actually only very few cases with genital dystrophy and no apparent endocrine involvement at the time.

3. Obesity in itself in these patients did not indicate that the case was or was not endocrine in nature. Rather, other more pertinent factors, such as mental, physical, somatic, or osseous deficiencies, were considered the criteria significant in determining whether the cases were endocrine, and in determining which was the primary offending gland involved.

4. In the two cases reported here, the primary offending gland responsible for the mental, physical, and genital disturbances was believed to be the thyroid gland. Therefore, a diagnosis of primary hypothyroidism with secondary involvement of the genitals was made.

5. With the use of proper and judicious hormone therapy, the non-obese boys with genital dystrophy responded favorably.

6. Of the various hormone preparations administered, the following results were noted: a. Anterior pituitary-like hormone extracted from pregnancy urine produced the best results. b. A gonadotropic hormone extracted from the anterior pituitary gland showed some gonadal stimulative properties. c. Anterior pituitary-like hormone extracted from the placenta showed no stimulative effects on the gonads of the one boy treated with this preparation. d. Desiccated thyroid administered to correct the hypothyroidism in hypothyroid patients showing genital dystrophy was found in cases of another series, in addition to other effects, to have stimulating effects upon the gonads. This gonadal stimulation, however, was less marked and much slower in its action than the stimulation with anterior pituitary-like hormone of pregnancy urine. Therefore, for more direct and rapid stimulation of the gonads, anterior pituitary-like hormone of pregnancy urine, rather than desiccated thyroid, was used to overcome the genital dystrophy.

7. For the correction of some of the other endocrine deficiencies as the mental, physical or osseous retardation noted in many patients in addition to the genital dystrophy, further therapy, such as desiccated thyroid, was found necessary. This is being given at this time in the cases reported here.

8. Since at the present time there is no definite way of determining beforehand when a patient will not respond to proper hormone treatment (although it is my opinion that the greater number of cases of genital dystrophy will respond to hormone therapy), it is advisable to institute such therapy in all cases of genital dystrophy, with the exception of cases of normally developed aberrant (ectopic) testicles. Then,

after judicious hormone therapy has been administered without results, surgery for the correction of a likely mechanical obstruction should be considered. If surgery is feasible, then afterward proper endocrine therapy should be resumed in order to provide the necessary gonadal stimulation.

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# THE FUTURE OF PEDIATRICS

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GOULD defines pediatrics as "the medical treatment of children." Whether we limit pediatrics to the definition of Gould or, as most of us would, give it a much broader interpretation, there is no question that the practice of pediatrics in some form or other will continue.

What concerns us is really not the future of pediatrics but the future of pediatricians. I do not wish to pose as a prophet; in fact, I am far better qualified to speak as an historian. I feel utterly unable to predict the future of pediatricians. I am quite certain, however, that the lot of pediatricians has been much better in the last forty years than it will be in the next forty.

The outlook is greatly obscured by recent political and social developments in this country. Are we headed toward a dictatorship? How far is the government going in the regulation of business, social security, and the regimentation of the lives of us all? Are all the activities pertaining to child health and child welfare, among both the well-to-do and the poor, to be taken over by the federal government and directed by Madam Perkins and Martha Eliot and their successors? If so, the average pediatrician is likely to become an employee of the state. If he is young and has been imbued with the spirit of the modern "youth movement" that the state owes him a living without his working for it, he will probably welcome the opportunity. Perhaps he will be better off financially if he is a government employee. Will he, however, lose his initiative and cease to progress? It is hard to tell. That government positions do not always stultify is evident from the discoveries which have been made by some of the physicians in the army, navy, and public health service.

Pediatrics is not a specialty like specialties dealing with diseases of the eye, ear, or skin. It simply deals with development and disease at a certain age. The pediatrician is really not a specialist. He is merely a general practitioner limiting his practice to early life. He does not know any more about children than does the general practitioner dealing with adults. He is not entitled, therefore, to charge more than other general practitioners. He cannot expect to get a specialist's fees.

The pediatrician of the past knew much more about children and their diseases than did the average physician. He still knows more, but not as much more, since, as the result of the improvement in the teaching of

Read at the fortieth anniversary of the founding of the Philadelphia Pediatric Society, Dec. 8, 1936.

pediatrics in our medical schools in recent years, all young physicians know much more about this subject than was the case in the past. This difference is bound to become less and less as the years go by.

Conditions have changed materially in recent years. The field of pediatrics, while increased in some directions, has been materially narrowed in others. Pure milk has practically put an end to the diarrheal diseases, the chief source of the pediatrician's summer income in the past. Pure milk, the general increase in knowledge among the laity as to the care of infants and children, improved hygienic conditions, and the absence of poverty as poverty used to be, have made infant feeding a relatively simple problem. It is fortunate that this is so, as the younger pediatricians know very little about what to do in difficult cases. Another one of the stand-bys of the past has, therefore, almost disappeared. Many infants and children of people who are able to pay small fees are being taken care of at welfare stations and baby hygiene clinics. This should not be. I wish some one would tell me how to stop it. The recognition and general use of the various vitamins have practically eliminated the diseases of nutrition. Immunization has almost entirely suppressed diphtheria and bids fair to do the same for other contagious diseases. This is a fine thing, but it was far more remunerative to the pediatrician to take care of sick children than it is to prevent them from being sick.

Every young practitioner knows the value of pure milk and understands the rudiments of the care of the well infant and child. No one thinks of starting in practice now without scales and a measure. Future physicians will know more. Any doctor can use a hypodermic syringe. Any doctor can prescribe the vitamins, if the mother is not already giving them. What does the pediatrician know about the treatment of colds and bronchitis and the various minor ills of childhood that the well-trained graduate of our medical schools does not or will not know? Will it really be necessary in the future, therefore, for people to employ a pediatrician to take care of well children or the minor ailments of childhood when the well-trained general practictioner can do practically as well? It will certainly be cheaper for them to have one doctor for the whole family.

In the past, general practictioners as a class have not been interested in superintending the care and development of well babies and children and have avoided it, probably in part because they did not feel qualified. In the future, when they will be better qualified and the problems will be much easier to meet, will they still be uninterested and glad to turn over the care and development of children to pediatricians? I do not know. I am inclined to think, however, that they will need the money.

It seems evident that the need for pediatricians is less now than it was in the past and that it will probably be less in the future than it is now. How about the demand for pediatricians now compared with that

in the past and in the future? The demand is unquestionably much greater now than it was in the past. This is due in part to the appreciation of what pediatricians have done to meet the need in the past and in part to the remarkable campaign of propaganda in behalf of the child and its welfare during recent years. The pediatricians have profited greatly from this campaign. It is the fashion now for people to employ pediatricians. The public demands them. Will this demand continue or increase in the future, although the need is less? Again I do not know. One thing, however, is certain. Even now the supply of pediatricians in our large cities is greater then the demand. If the supply of young pediatricians continues to increase in future years as it has in the last few years, it will soon be the same everywhere. The saturation point will soon be reached.

There will be a need for a certain number of experts in pediatrics in the future as in the past—men who will know as much more about the diseases of early life than the average pediatrician, as the old-time pediatricians, like Jacobi, Holt, Rotch and Griffith, knew more than the general practitioners of the past. These men will be the consultants. The demand for consultations will never be as great again as it used to be, however, because of the improvement in the general health of children, the better education of general practitioners in the care and treatment of children, and the great increase in the number of pediatricians. They will naturally be men living in the large cities and connected with large hospitals, where they can see and study a vast number of sick children. They will probably also be teachers and must be familiar with all the advances in diagnosis and treatment in pediatrics. Men who have been brought up in, who have practiced entirely in, hospitals and who have devoted themselves exclusively to teaching and research do not, however, usually make good consultants outside of the hospital because they are quite likely not to appreciate the problems met in private practice and to be at a loss when they are not in their laboratories. On the other hand, men who are spending much of their time in practice and who are familiar with the problems met in practice, but who are not closely connected with teaching and research, are not likely to have a broad enough knowledge to deal with obscure cases. Men will be needed who have held and continue to hold hospital positions, who are familiar with research, but who are also familiar from personal experience with the problems of private practice and with the conditions under which doctors carry on their work and people live in their homes. Such a combination was possible in the past when pediatrics was less complicated and there were not so many full-time men in the hospitals. Let us hope that it will be in the future. The compensation for such men should be large. It is possible that two kinds of consultants will be developed, one to whom cases of chronic and obscure illness will be re-

ferred for diagnosis and treatment in a hospital and another who will be called to see patients with acute illness in their homes.

There will also undoubtedly continue to be opportunities for pediatricians as teachers and investigators. Whether the present system of full-time professorships in the clinical branches will continue or not, no one knows. At any rate, there will never be many of these places. Those holding lower full-time teaching positions can never hope to get large salaries. The type of man who holds such a position is, however, usually not as much interested in the financial return as in his work. There always have been such men and probably always will be.

It looks as if the interference of government with business, excessive taxes, and the various experiments as to the redistribution of wealth will prevent any further large contributions to medical schools, hospitals, and other charitable undertakings. This will necessarily curtail the development of research in pediatrics and diminish the opportunities for pediatricians and others along this line. In some ways this may be a blessing in disguise as it may prevent a lot of useless, pseudoscientific, so-called research, and diminish the output of *Arbeits*. While it may hamper, it will not, however, stop the real scientific investigator. He will keep on at any cost. Let us hope that there will be enough funds still available to enable him to do so.

It is evident that the opportunities for pediatricians will not be as great in the future as they have been in the past. Forty years ago pediatrics was a virgin field; now it is overcultivated. The other end of life now offers the greatest field for development. There are more old people than there used to be, and almost all of them are ill in some way or, at any rate, are wearing out; they like many visits; they are more interesting than children; the doctor is not blamed when they die; and the estate pays the bill. The parents of children are usually young, are just starting life, and are, consequently, short of money. Many of the aged have accumulated money. They are always willing to spend it in order to be comfortable and to live longer. If the Townsend Plan is adopted or the new measures for social security are continued, old people will be the only ones who will have any money. My advice to young physicians is, therefore, to take up geriatrics, not pediatrics.

# Critical Review

## DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

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AS KNOWLEDGE increases, the intimate relationship between the glands of internal secretion becomes more and more evident. Clinically, according to Long,[1] the "condition that follows hypo- or hyperfunction of an endocrine organ is not merely due to a loss or phthora of that particular internal secretion, but is a result of the disturbance of the normal hormonal equilibrium of the body."

This equilibrium depends not alone upon the amount of hormone secreted, but also upon the state of the organ or tissues upon which it acts. Thomson[2] and his coworkers report that they are able to temporarily increase the basal metabolic rate of some individuals by the administration of thyrotropic principle of the pituitary. Since the thyrotropic hormone is without effect on the basal metabolism after total thyroidectomy, this action of the pituitary hormone must result from stimulation of active thyroid gland substance. Hertz and Oastler[3] report an increase in the thyrotropic principle in the blood serum and urine of patients with myxedema but no increase in patients with thyrotoxicosis. Friedgood,[4] in a study of the effect of anterior pituitary extract on the thyroid, reports that the thyroid gland does not respond indefinitely to this stimulus. On the contrary, he contends that prolonged stimulus leads to a cyclic type of response wherein hyperfunction alternates with hypofunction. Such evidence indicates that the receptor is an important factor in the general endocrine balance, even though its full significance is not yet apparent.

It has long been recognized that the nervous system may influence the activity of an endocrine gland. Cannon's experiments on the adrenal medulla have shown beyond dispute that stimulation of splanchnic nerves causes that organ to secrete adrenalin in large amounts. That a similar relationship may exist between the nervous system and other endocrine glands seems probable. It is well established that the anterior hypophysis is responsible for the initial maturation of the ovarian follicles. Dandy has shown that the sympathetic innervation of anterior hypophysis is derived from the cervical sympathetic ganglion. Friedgood and Pincus[5] present evidence that in rabbits faradic stimulation of the cervical sympathic will stimulate the pituitary to secrete gonadotropic hormones which in turn cause maturation of ova and ovulation. Future studies on the influence of the nervous system on endocrinopathies may reveal other similar relationships which may be of clinical importance.

A further factor influencing the action of the secretory glands according to Bock[6] is the acid-base equilibrium of the animal organism. His experiments on infantile female mice indicate that smaller doses of ovarian hormone were needed to elicit estrus when the animals were

placed on an acid diet than when on an alkaline diet. He obtained similar results when he experimented with the gonadotropic hormone. These findings suggest another relationship between diet and hormonal activity. The effect of vitamins has already been commented upon in earlier reviews. The reopening of the possible connection of diet to hormonal activity further complicates the problem of bringing into orderly array the various influencing factors. It seems possible that development of this knowledge will supply means of prevention as well as influence the therapeutic methods used in treatment.

Another factor of importance in endocrine therapy is the route of administration. Hisaw and others[7] discovered that an anterior pituitary powder which caused only follicular development in the ovaries of monkeys after subcutaneous administration would luteinize the ovarian follicles when administered intravenously.

The examples mentioned emphasize again how intricate the relationships are between the various glands, and it should not be necessary to warn clinicians against the use of glands concerning which they do not possess a full knowledge of all their possible actions. Such therapy should be left in the hands of those with special knowledge. Some of the hormones are closely related to carcinogenic substances.[8] Unless the potential dangers of hormone preparations are recognized, some "new therapy" may prove not only inefficient, but dangerous.

*Basal Energy Metabolism.*—Clinicians who deal with the basal energy metabolism of children must be familiar with the physiologic factors which influence the production of heat. A discussion of these factors will show that a "hit-or-miss" choice of standard of reference and improper technic in making measurements will yield results which are confusing to the clinician and which may and often will lead to conclusions which subsequent clinical experience fails to justify.

New light has recently been thrown on the subject which may help explain some of the seeming discrepancies in clinical results. N. B. Talbot[9] used the twenty-four-hour urinary output of creatinine as a measure of active protoplasmic mass in the body. He found a close correlation between it and the heat production. Since there is also a close correlation between the creatinine output and the weight of average normal children, these findings support F. B. Talbot, Wilson, and Worcester,[10] who found a close correlation between heat production and weight of girls of all ages. Lewis, Kinsman, and Iliff[11] misunderstood the experimental condition of the children reported by F. B. Talbot and others[10] when they said that "they were based upon tests on both sleeping subjects and awake subjects and the proportion of each in the different groups is unknown." This statement which has unfortunately appeared several times in the literature due to careless reading of the original papers is here corrected. The children under two years of age were asleep in practically all instances. Those over two years of age were awake in most cases. Those over five years of age were awake in all tests.

Comparison of the data obtained in different parts of the country and the world shows that, barring different experimental conditions and degrees of basality, the amount of heat normally produced is higher in some locations than in others. It may be said that there is in general a trend for the heat production to be higher in temperate climates and to diminish as tropical climates are approached. An example of the difference which may be found in the temperate climate

is that the metabolisms of Boston girls tend to be about 7 per cent lower than those of girls living in Denver, Colorado.[11] It is obvious then that the standards of metabolism used in any community should be corrected for the place in which they are used. Correction tables for height and weight standard for girls have been given by Talbot, Wilson, and Worcester.[12]

Evidence is accumulating that there is no racial difference in heat production but that the surrounding temperature affects the level of the metabolism.[13] F. B. Talbot has shown that the metabolism is relatively 3.8 per cent higher in girls who are moderately underweight and 4.4 per cent lower in overweight girls than the standard average. This should be taken into account in interpreting any metabolism results. Rapid growth in height may elevate the normal metabolism; therefore due allowance should be made for this fact in rapidly growing children. Dietary intake appears to affect the basal metabolism. Johnston and Maroney[14] have shown recently that there is a definite lowering of the metabolic level with submaintenance diets. They have shown that an adequate diet with a high increment of protein is followed by a marked increase in the metabolic level.

After the factors described above are considered, the following table may be used in the clinical interpretation of basal metabolic measurements when the standard used is total calories for weight.

TABLE I

| | |
|---|---|
| Normal range | −15% to +15% |
| Suspicious range | −20% to −15%; +15% to +20% |
| Definitely lowered metabolic level | Below −20% |
| Definitely elevated metabolic level | Above +20% |
| Basal metabolic level is lowered | Hypothyroidism |
| | Hypoadrenalism (rare) |
| | Hypogonadism (probably) |
| | Hypopituitarism ? |
| | Marked inanition (rare) |
| Basal metabolic level is raised | Fever (approximately 7% for every degree Fahrenheit) |
| | Hyperthyroidism |
| | Leucemia |

*Choice of Standards.*—The writer[13] has frequently discussed and shown evidence why the use of the standards of total calories for weight and for height are his choice. The use of these standards with abnormal cases has been found to lead to fewer clinical errors than the use of more complicated standards. It therefore seems logical to recommend for clinical use the simple total calorie standard for children. Those who believe in the more complicated standards should produce evidence that the standards of surface area or those requiring the use of other formulas give results sufficiently better to justify their use. The statistical studies of Talbot, Wilson and Worcester when applied to data obtained from many sources did not show that these formulas resulted in superior accuracy.

*Thyroid.*—Numerous attempts to measure the activity of the thyroid gland by methods other than basal metabolism are reported in the current literature. One of these is founded on the theory that iodine is intimately concerned with the function of the thyroid gland. Perkin, Lahey, and Cattell[15] and independently Watson and Barber[16] propose an iodine tolerance test which they feel may be of diagnostic aid in

establishing abnormal activity of the thyroid gland. The blood cholesterol is also proposed as an index of thyroid activity. A recent report of Schnitker, Van Raalte, and Cutler[17] does not offer very encouraging support of the cholesterol index.

Age appears to be a factor in the resistance of the organism to thyroxine. Working with rats, Bodansky and Duff[18] show that young animals stand doses of thyroxine which cause rapid loss of weight and death in older animals. They also show that hyperthyroidism is associated with a loss of muscle creatine. Thorn[19] reports studies in human thyroid disorders. He alleges that there is a decreased tolerance to administered creatine in thyrotoxicosis. Poncher[20] has demonstrated an absence of physiologic creatinuria in cretinism and childhood myxedema together with an increased tolerance to ingested creatine in children with hypothyroidism. It appears that normal creatine metabolism is restored by thyroid medication before there is a detectable change in the energy metabolism.

*Parathyroid Gland.*—Shelling[21] points out that hyperparathyroidism can occur in young children with generalized osteitis fibrosis cystica. The earliest symptom may be calcium phosphate renal calculi. The disease may be confused with glomerulonephritis. Elson[22] points out that the blood phosphorus may not be abnormal. It is suggested by Goadby and Stacey[23] that the parathyroid may act directly on the kidney to produce a phosphorus diuresis. Morgan and Samisch[24] likewise postulate a direct action on renal tissue.

In the treatment of postoperative parathyroid insufficiency Boothby and Davis[25] recommend that soluble calcium salts be administered in large doses, that the diet be low in phosphorus, and that vitamin D be administered in reasonable dosage. Overdosage must be avoided. Parathyroid extract should be administered only occasionally.

*Thymus.*—In the last review, mention was made of the brilliant work reported by Rowntree and his associates on the physiology of the thymus. Einhorn and Rowntree[26] report further observations on the biologic effects of thymectomy. Thymectomy in successive generations of rats results in a definite retardation in the rate of growth. The average retardation in growth is 36.9 per cent at thirty days. After seventy days, the growth curves conform to normal. The rate of development is not materially affected. Hanson's thymus extract causes the growth curves of thymectomized animals to correspond with those of the controls. In children, according to Boyd,[27] involution of the lymphoid tissue in the cortex of the thymus begins at the age of four years. The medulla with Hassall's corpuscles begins, like the whole thymus, to involute at puberty. In acute infections, accidental involution progresses markedly within one week except in exophthalmic goiter when the parenchymatous structures are hypertrophied. A future correlation between animal and human thymus physiology should prove extremely interesting.

*Pineal.*—Rowntree and his coworkers[28] make further reports on the effect of injections of pineal extract intraperitoneally into successive generations of parent rats. The result is a decrease in the birth weight and rate of growth, together with an accelerated rate of differentiation and development. The effect becomes more marked in succeeding generations. A similar premature physical and sexual development is noted by Horrax[29] in preadolescent human beings. He points out the interesting fact that the two largest mammals have no pineal body.

*Adrenal Gland.*—It may be pertinent to repeat a warning sounded in an editoral of the *Journal of the American Medical Association.*[30] The writer pointed out that there are many delicate structures adjacent to the adrenal glands. In most instances there are no real indications for operative or x-ray therapy on the adrenal glands.

A relationship may exist between neurosis and adrenal cortical function. In animals Liddell, Anderson, Kotyuka, and Hartman[31] show that cortical extract influences experimental neurosis. It quiets sheep suffering from neurosis and at the same time improves the vigor of the animal as a whole. The effect appears to be opposite that of epinephrine. The effect of cortin persisted twenty-four days in their experiments.

Bruch and McCune[32] have studied the involutional changes in the adrenal glands in newborn infants. The adrenals normally undergo extensive morphologic changes during the first year of life. They are unable to find any biochemical changes of the sort associated with Addison's disease during the period of most extensive reorganization of the gland.

Friedman[33] reports a case of tuberculosis of the adrenals in a child of twelve. Although there was no pigmentation, there was profound asthenic, marked circulatory weakness, and gastrointestinal disturbances. He suggests that tuberculosis of the adrenals may not be so infrequent as the scarcity of reports would indicate.

*Gonads.*—It is of interest that the ovary contains both male and female anlage, while the testes contain only the male anlage. The androgenic substance (male producing) produced by adrenal cortical tumors thus causes sex reversion in the female only. Arrhenoblastomas of the ovary have a similar effect. They cause defeminization and masculinization characterized by male contour, penilelike clitoris, hirsuties, amenorrhea, and flat atrophic breasts. On the other hand, granulosa cell tumors of the ovary cause precocious puberty and menstruation in young children by the production of estrone. Baldwin and Gafford[34] give a summary of the cases of arrhenoblastoma reported to date.

Cameron[8] gives an excellent review of reproductive hormone chemistry and the endocrine control of human reproduction. The following is quoted freely from his book: The pituitary gonadotropic hormone, prolactin, and the anterior pituitary-like hormone are protein in character. Estrone (female group), progesterone (corpus luteum), and testosterone (male group) are cholesterol derivatives and are crystalline pure substances.

In the male the pituitary causes the testicles to develop and descend into the scrotum. Associated with puberty is the appearance of spermatogenic activity and testosterone (interstitial tissue product) which causes the prostate and seminal vesicles to develop together with other secondary sex changes.

In the female, the pituitary causes an increase in the size of the ovaries and in the proportion of graafian follicles. At puberty growth of the follicles is rapid and is associated with an increase in blood estrone. The circulating estrone stimulates the development of secondary sex characteristics. Eventually a follicle ruptures; its leading competitors atrophy but still produce estrone. Estrone causes a proliferation of the basement membrane of the uterus. It also depresses the gonadotropic function of the pituitary. The ruptured follicle de-

velops into a corpus luteum which produces progesterone. While progesterone is circulating, follicle growth is depressed, possibly because of a previous influence of estrone on the pituitary or because of a combined action of estrone and progesterone. Progesterone causes the proliferated uterine basement membrane to become glandular. During the fifteen days following the rupture of the follicle, the corpus luteum waxes and wanes and with it the progesterone. When the circulating progesterone falls sufficiently low, its control on the uterus is lost and the physiologic hemorrhage of menstruation occurs. At about the time of menstruation, the level of estrone and progesterone falls sufficiently to release the pituitary so that it may again exert its gonadotropic action.

*Protamine Insulinate.*—One of the most important of the recent advances in endocrinology is protamine insulinate. Hagedorn and others[35] of Copenhagen produced a relatively insoluble compound of insulin with protamines which has an isoelectric point at a pH approaching that of body tissues. Because of its relative insolubility it is absorbed slowly. As a consequence, the blood sugar lowering effect persists about twice as long as ordinarily. Because of its slow rate of absorption it works too slowly for diabetic coma and too slowly to overcome the hyperglycemia of a large meal. It is thus an adjunct to old insulin and is not meant to supplant it.

Root and his associates[36] report their clinical experience with protamine insulinate. They emphasize that the drug is still in the experimental stage and that further work is needed to show when and how it is best used. Hagedorn and his associates ordinarily give a dose of regular insulin in the morning and a dose of protamine insulinate in the evening. He points out that as now used the compound is not indefinitely stable.

Butler[37] describes a simple dietary regime for diabetic children. It is founded on the principle of first prescribing an appropriately and properly balanced diet subject to limited fluctuations in composition and calorie content, and then, second, giving insulin to establish proper carbohydrate metabolism.

He believes that there is no need to initiate treatment without insulin or to determine the patient's sugar tolerance. No increase in the ultimate tolerance of the patient is obtained by placing the patient on submaintenance diets for a period of time. He recommends the following diet: (a) no candy, cakes, cookies, jams or sugar, and no desserts to which such ingredients have been added in any considerable amount; (b) only one piece of bread a meal or its equivalent in crackers; (c) at one meal only one of the following—rice, macaroni or potato, and of the one only a moderate helping; (d) only half a banana or apple at any one time; (e) in middle of morning some food containing between 10 and 20 gm. of carbohydrate. If at any time symptoms of hypoglycemia appear, the juice of one orange or some food containing 10 gm. of glucose is to be taken immediately; (f) except for these instructions the patient may eat as desired at mealtime provided ordinary common sense is used.

*Pituitary.*—Wislocki and King[38] present a beautiful study on the vascular supply to the hypophysis. The hypophyseal stem does not receive any veins from either anterior or posterior lobe. Their work indicates that the "pituitary gland is not intimately connected with the surrounding neural centers or other parts of the hypothalamus,

either by demonstrable interstitial pathways or by vascular connections. The infundibular stalk is, on the other hand, intimately connected with the anterior lobe of the hypophysis by portal veins."

Marble[39] describes the use of a posterior pituitary powder in the treatment of diabetes insipidus. It is administered intranasally and is recommended because of its ease of application and low cost.

Shelton, Cavanaugh, and Evans[40] report that a growth-promoting hypophyseal extract is disappointing from the clinical standpoint. It does not rehabilitate the classic dwarf, but it may be useful in stimulating growth of dwarfish persons during the growth period if they are not losing over 50 per cent of the normal growth increment. Although they observed no refractory state and no interference with puberty, they point out that there is some physiologic danger associated with its administration. When injected intramuscularly, it stimulates growth in direct ratio to the amount of extract administered.

McQuarrie, Thompson, and Ziegler[41] report that they are able to reduce edema under certain conditions by the alternate administration and withdrawal of the antidiuretic principle of the pituitary gland. They do not understand the mechanism of the response.

Further evidence is accruing on the side of those who believe that the so-called antigonadotropic substances are not true antihormones, but are protein antibodies. DuShane and his coworkers[42] report an experiment in which they unite female rats parabiotically, and then hypophysectomize one of each pair and castrate the other. This experiment shows that, when one rat has her ovaries constantly stimulated by the gonadotropic hormone produced by another rat, no evidence of antihormone formation is found. Twombly[43] finds protective substances in the serums of rabbits who have received repeated injections of human pregnancy urine hormone which he feels are probably protein antibodies.

*Dwarfs.*—The observations of Malvina Hofman[44] on the pigmies of Africa may be quoted in her own words. "These little people resemble the Negritos in the Malay jungle, in the Philippine Islands, and the Andaman Islands. Their crinkly short hair is an easily recognized characteristic. They are not deformed as one might suppose, although they are sometimes only three feet eight inches tall, but generally the males vary from four to nearly five feet. They are stockily built and strong. I wonder if their pituitary gland system is built on the same principle as in Shetland ponies. These are also undersized but in good proportion, and never grow up into real horses. Apparently when the babies are born they are normally proportioned, but after a few years they stop growing and they stay the size that a white child of seven or nine years might be.

"Of course, these Huri people live on the meager regime enforced upon them by the jungle—nuts, herbs, roots, occasional juicy morsels of small wild birds and game. When good fortune comes their way, the tribe settles down around the body of a dead elephant, killed by one of their diminutive tribal heroes. . . .

"The children suffer seriously from lack of good nourishment during the first years of their life. Their bones do not grow hard enough to carry their weight, and the result is rickets and many other diseases that serve their primitive purpose of weeding out the unfit, and permitting the survival of the fittest."

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# American Academy of Pediatrics

## Proceedings

### SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MO., MAY 11 AND 12, 1936

### Round Table Discussion on Intestinal Parasitic Infestations in Children

Chairman: Ernest Carroll Faust, Ph.D., New Orleans, La.
Assistants: H. L. Dwyer, Kansas City, Mo.
Horton Casparis, Nashville, Tenn.

#### Intestinal Parasitic Infestations in Children

**Ernest Carroll Faust, Ph.D.**

In a broad sense parasitic infestations involve invasion of an organism by all types of life, including bacteria, filtrable viruses, fungi, protozoa, helminths, and arthropods. In the more restricted sense of the term, parasitic infestations are considered to be of animal parasite origin. Our discussion will be limited to this more circumscribed field, which in itself includes more than a hundred etiologic agents parasitizing man. However, we shall discuss only a few of the more important intestinal diseases produced by protozoan and helminthic agents. I have been particularly interested in these diseases as they affect children, and am especially honored to be asked to conduct this round table discussion of the American Academy of Pediatrics.

In each of these infestations to be presented, an attempt will be made to review briefly the following aspects of the problem: (1) the offending organism, its incidence, its stage or stages infestive for man and its portal of entry into the human body; (2) the site or sites where the parasite lodges in the body, together with the local and systemic tissue involvement and reactions; (3) the symptomatology of the disease produced; (4) diagnosis of the infestation; (5) therapeusis; and (6) prevention.

*Protozoan Infestations*

1. *Amebiasis.*—This disease is produced by *Endameba histolytica,* the only parasitic ameba of man known to be pathogenic. We are coming more and more to realize that amebiasis is not confined to the tropics but is also widely distributed throughout temperate climates. As Craig[1] has indicated, it is safe to estimate that at least 5 per cent of the population in the United States is infested with this organism, although a relatively small proportion of this infested population is at any one time suffering from acute amebic dysentery. A considerably larger number presents evidence of chronic amebiasis, with vague and generalized intestinal and systemic symptoms, while the largest percentage of all consists of so-called "carriers," who harbor the organism in their intestinal tract without definite manifestations. Nevertheless, all clinical evidence favors the view that *E. histolytica* is always a tissue invader.[1]

The potential location of amebiasis in the intestinal tract coincides with that of bacillary dysentery, namely the entire large bowel and the posterior portion of the ileum. However, the local and systemic pathology and symptomatology of these two diseases are essentially different. In amebiasis the onset is usually gradual and there is no fever; in bacillary dysentery the onset is usually sudden and a pyrexia is common. In amebiasis the lesions are typically discrete, bottle shaped, pinpoint or chemise-button type at the surface and enlarged, frequently undermined and confluent at the base, extending through the mucosa into the submucosa, frequently into the muscular coats and occasionally perforating through the serous layer. Typically there is no local or systemic reaction. In bacillary dysentery the lesions are confluent, inflamed and hyperemic, and confined to the mucosa. There is an active local and systemic polymorphonuclear leucocytosis. In acute amebiasis the stools are dysenteric, but there are few leucocytes. In bacillary dysentery the leucocytes and macrophages are conspicuous in the exudate. In amebiasis complement fixation is specific; in bacillary dysentery specific and subspecific agglutinization occurs.

The initial lesions of amebic enteritis usually appear in the cecum and appendix, and are more common at these levels of the large bowel than they are in the sigmoid colon and rectum.[2, 3] In fact, amebiasis is not uncommonly present in the cecum and appendix when proctoscopic or sigmoidoscopic examinations are negative. Probably less than 50 per cent of amebic lesions occur in the lower colon and rectum.

The active case of amebic dysentery is one which is discharging the trophozoite stage of the organism in a bloody mucous exudate. In such an exudate the amebae rarely, if ever, encyst, either before or after they have left the bowel, and under such conditions are not a source of infestation for other persons. On the other hand, amebae passed in formed stools are almost invariably encysted and constitute the real menace of infestation for other individuals. It is particularly important to keep this fact in mind, since stools of this type are usually passed by "carriers" or other persons who at the time are not suffering from evident symptoms of dysentery or diarrhea, and are therefore not recognized as potential sources of infestation for other individuals. For specific diagnosis such cysts require differentiation from those of *Endameba coli, Endolimax nana* and *Iodameba bütschlii,* nonpathogenic species which commonly inhabit the lumen of the large bowel. In my opinion this diagnosis is not an easy one; at times it requires all the skill and experience which years of contact with the subject afford.

Amebic enteritis in children is not as common as it is in adults. Referring to the dysenteric type of the infestation, DeBuys[4] in 1914 stated that it is "a relatively rare disease in children, not because children are not susceptible to the infestation but because they are less exposed to the etiologic factors which cause the infestation in the adult. It is possible that in children it may exist much more often than is believed but may escape detection. . . . The younger the child, the less often is the disease found. . . . As they grow older the exposure, and consequently liability to infestation, is greater. . . . The symptoms of amebic dysentery in children do not differ from those in the adult." These statements, made several years before the importance of cysts and "cyst passers" had been demonstrated, not only are as true today as when they were written, but seem almost prophetic in their significance. At the time DeBuys wrote, amebic dysentery in the Charity Hospital, New Orleans, had been diagnosed in 0.34 per cent of nearly 100,000 cases over a period of eight and one-half years. In his pediatrics service in the Touro Infirmary only four out of 3,000 cases (0.133 per cent) had been found with amebic dysentery. Utilizing present-day methods of diagnosis, including concentration technics for the cysts, Faust and Headlee[5] have found that the average clinic population of the New Orleans metropolitan area has an expected *Endameba histolytica* incidence of 13.2 per cent, while

Faust and King[6] found 17.7 per cent infection in mothers near term in the Charity Hospital. These records are considerably lower than those recorded by Faust[7] for a population group in Wise County, Virginia, and by Meleney, Bishop and Leathers[8] for rural populations in Tennessee and are decidedly lower than the figures obtained by Faust[9] for native Panamanians. Moreover, in Wise County, Virginia, Faust[7] found an infestation of 16.5 per cent in children under 5 years of age and 20 per cent in those from 6 to 15 years old, although the two youngest children infested were each three years old. Likewise, in an intensive study of a rural community in Tennessee, Milam and Meleney[10] discovered no infestation in children under two years of age, in spite of the fact that 20.7 per cent of those children up to and including the fourth year of life were infested, and 35.0 per cent of those from 5 to 9 years of

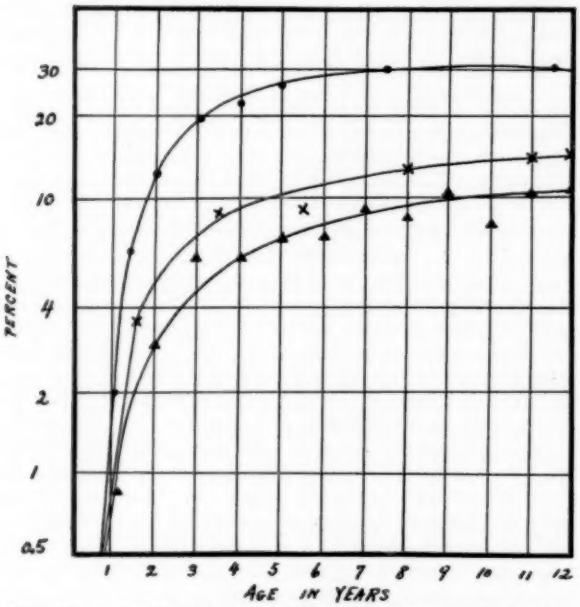


Chart 1.—Percentage distribution by age of amebiasis in New Orleans (▲), Tennessee (×), and Panama (●).

age harbored the parasite. In contrast to these high incidence data Summerlin[11] found only 0.4 per cent infestation with *E. histolytica* in children seen in private practice in California. Thus there appears to be a marked difference in the incidence figures of amebiasis in children, depending in part on the geographical location of the group of individuals studied, and in part on the economic condition, the personal hygiene and the sanitary conveniences of the community. Nevertheless, in certain of these population surveys, in which it has been possible to plot curves showing the age incidence of amebiasis (Chart 1), it has been found that the curves are qualitatively the same, although quantitatively different. During the first year of life the incidence rate is low, in fact practically negligible. The rate increases by degrees, depending on the type of environment, until puberty, when a maximum infestation is reached. Thus present-day information on amebiasis in children, although amplified to include chronic and carrier cases as well as acute infestations,

confirms the original views of DeBuys[4] that amebiasis is not as common in children as it is in adults, and is rare in infants under two years of age.

Nevertheless, it is not sufficient, in the light of present-day knowledge, to consider as important only those cases of amebiasis in children who have definite dysenteric symptoms. Aside from the public health importance of the "carrier," the positive diagnosis of *E. histolytica* cysts in the stools of nondysenteric children requires individual attention, since at any time "carrier" condition may become acute, and the possibility of amebic liver abscess in persons without a previous history of amebic enteritis must always be considered. Furthermore, there are those children with intestinal symptoms centering in the region of the appendix, in whom there is no evidence of dysentery and in whose stools cysts of *E. histolytica* are not found after repeated examination. In a considerable proportion of these cases I have obtained positive diagnosis for *E. histolytica* by examining the mucous discharges immediately following a high enema of tepid physiologic saline solution. Apparently in such cases there is a chronic amebiasis of the cecum or appendix, the amebas discharged from the lesions die and disintegrate in transit down the bowel, and the absence of diarrhea or dysentery leaves no direct clinical evidence of amebic infestation.

In all individual cases of amebiasis, whether acute, chronic or "carrier" in type, specific therapy is indicated. Possibly emetin by vein is still the drug of choice for dysenteric manifestations of amebiasis; it is particularly helpful in reducing the number of stools and in relieving griping and tenesmus. There is some doubt, however, as to whether emetin is actually curative within the limits of safety to the patient. According to Leake[12] (*vide* DeBakey and Ochsner, 1935) a total of not more than 10 mg. of the drug per kilogram of body weight is the maximum safe dosage. For the subacute, chronic and "carrier" types of the disease chiniofon or vioform is effective and much less toxic than emetin. Chiniofon is usually sold under the trade names of "anayodin" or "yatren." Chemically it is sodium iodoxyquinolin-sulphate. It is supplied in 4 grain (0.25 gm.) enteric coated tablets and is nontoxic in therapeutic doses when administered orally, which is the preferred route. The adult dosage is 3 to 4 tablets three times daily. For children one to 3 tablets thrice daily may be given safely, depending on the patient's age. Meals need not be modified or interrupted. There is frequently a diarrhea which accompanies this treatment but this is no contraindication for its continuation. A complete course of treatment covers eight to ten days. Vioform is iodochloroxyquinoline and is administered in powdered form in 4 grain gelatin capsules. For children one to three capsules three times a day for eight to ten days is recommended, followed by a week's interval and then the course is repeated. It is not toxic in therapeutic amounts when administered by mouth. Carbarsone has apparently proved its efficiency in "carriers" but possibly is not as satisfactory in the more involved types of the infestation. Carbarsone is 4-carbaminophenylarsinic acid. Its dosage and method of administration are similar to vioform. In therapeutic amounts it is not toxic. With this choice of satisfactory therapeutics there is no present-day excuse for the administration of ipecac or bismuth. As a dietary adjuvant liver by mouth will undoubtedly prove helpful, since its amebicidal properties are relatively high[13] and its value in stimulating erythropoiesis is well established.

In considering prophylayis in amebiasis the epidemic spread of the disease by water must not be confused with endemic amebiasis. The Chicago hotel epidemic of 1933-34 was unquestionably water-borne, as were the epidemics in the Philippines and in the Panama Canal Zone before the completion of sanitary water systems. Such epidemics do not explain the widespread distribution of amebiasis through the world, with the great majority of infested persons in the class of "symptomless

carriers.'' How then is this widespread endemicity explained? It is believed to be due to contamination of food by unclean ''carriers,'' but this has never been definitely proved. Until actual proof is furnished, control of the infection in its endemic form is not rationally possible or practical.

2. *Flagellate Infestations.*—The intestinal flagellates of man include three common species, *Giardia lamblia, Chilomastix mesnili,* and *Trichomonas hominis,* as well as several rarer forms and numerous contaminators. Of this group *Giardia lamblia* is unquestionably the most common species found in children. I have had an opportunity to study the incidence of this infestation in several localities in the Western Hemisphere, including New Orleans, Wise County, Virginia, Panama and Puerto Rico. In New Orleans the data cover surveys of the ambulatory clinic population and of children domiciled in asylums. These data are all consistent with those obtained by Meleney, Bishop and Leathers[8] in Tennessee, and indicate that the rate of acquiring this infestation is greatest during the first two years of life and that the peak of the incidence curve is reached before the fifth year of age, after which the incidence rate falls through later childhood and adolescence to approximately one-fourth of its maximum, and remains thereafter about on the same low level throughout life. In other words, young children are highly susceptible to infestation with this parasite, but after five years of age they begin to acquire some resistance to it. About three-fourths of the children who acquire the infestation may be expected to lose it before they mature. What clinical information do we have about this infestation, which is essentially one of childhood?

The organism lives and multiplies at the levels of the duodenum and proximal jejunum, where it may be attached by its ventral sucking surface to the mucosa. Except in cases of frank watery diarrhea it is discharged from the bowel in the encysted condition and the resistant cyst serves as the source of infestation for other individuals. As far as is known this flagellate does not invade the tissues, but when present in myriad numbers produces a superficial irritation (and erosion?) of the cuticula of the duodenal epithelium, which is probably responsible for the mucous diarrhea in such patients. Under such conditions it may be regarded as mildly pathogenic. There is also suggestive evidence, but little actual proof, that these organisms may migrate through the ampulla of Vater up into the common duct, the proximal biliary tract and the gallbladder. Certain it is that in chronic cases there is an associated duodenitis and that the organism stubbornly resists chemotherapeusis, although the majority of the parasites may be evacuated by weekly purgation with Glauber's salts.

In contrast to Giardia, *Chilomastix mesnili* is not typically acquired by the child as early in life and rarely, if ever, reaches the high incidence peak of Giardia. Chilomastix lives in the lumen of the cecum. There is no proof that it is a tissue parasite or that it produces any irritation of the cecal epithelium. It may be discharged from the bowel either in the active or in the encysted stage. It encysts readily outside the bowel and is apparently quite resistant in the cyst form, which is the infestive state.

*Trichomonas hominis* is also a parasite of the cecum. Most protozoologists regard it as a different species from *T. buccalis,* which lives in the mouth, and from *T. vaginalis,* which is recovered from vaginal discharges and from the urine. There is no proof that it invades living tissue, although it has been found ingesting free erythrocytes[14] as well as in the intestinal wall postmortem.[15] When it is present in the feces it may more properly be regarded as an index of gastrointestinal disturbance rather than an etiologic agent of disease. This flagellate does not encyst and its passage through the stomach into the intestine can only be conceived to occur in patients with gastric anacidity or when ingested in a menstruum such as milk.

*Helminth Infestations*

1. *Ascariasis.*—This infestation is produced by the large intestinal roundworm, *Ascaris lumbricoides,* which has a cosmopolitan distribution but is most common in warm climates. Its highest incidence and the greatest worm burden occur in children under ten years of age. In the United States heavy infestations with this worm are found throughout the hill districts of the South, from the western part of Virginia to Missouri. Outside this area heavy endemic foci occur only in the families of Cuban cigar workers in Tampa, Florida, and in central south Louisiana,[16] but its importance in children's clinics is established throughout the South, and from time to time it is reported endemically from other portions of the United

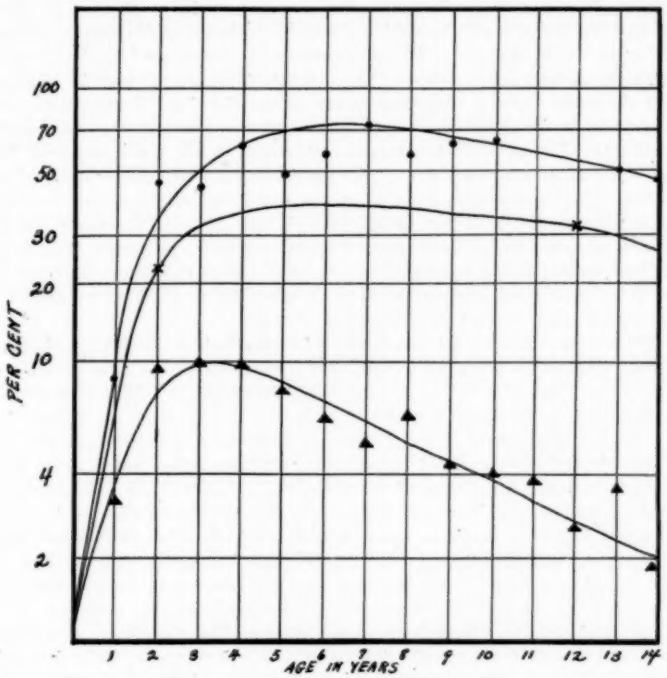


Chart 2.—Percentage distribution by age of ascariasis in New Orleans (▲), Tennessee (×), and Wise County, Va. (●).

States. The age incidence of this infestation in three Southern areas is illustrated in Chart 2. These worms live free in the lumen of the small bowel, where the female lays about 200,000 eggs *per diem.* If the female has been fertilized, these eggs are usually viable. When discharged in the feces, they require several weeks to complete embryonation. They are very resistant to unfavorable environmental conditions, and once fully embryonated they may remain viable for many months. Such embryonated eggs (and not those recently discharged in the feces) are the infestive stage for man. Upon being swallowed the eggs pass down through the esophagus and stomach into the small intestine, where they hatch and the motile larvae crawl out. They penetrate through the intestinal wall into the mesenteric lymphatics or mesenteric venules and are passively transported in the blood stream through the right heart to the lungs. Here several days are required for them to

break out of the pulmonary capillaries into the air spaces, after which they are carried up the respiratory tree to the epiglottis and are then swallowed. On arrival in the small intestine, they grow to maturity. From the time of exposure until eggs are discharged in the stools five to seven weeks are required.

The symptoms produced by this worm are due to several factors, including the intensity of the infestation, the susceptibility of the patient to toxic by-products of the worms, and to other factors, as yet unknown. In transit through the lungs, particularly following heavy exposures, congestion of the lobules frequently results, so that the syndrome simulates bronchial and lobular pneumonia.[17] The adult worms in the intestine usually produce no dramatic symptoms, the most usual complaint being an intermittent sharp colicky pain in the epigastric region.[18] However, it has been demonstrated that on the average ascariasis retards both physical and mental development of the child.[19] Moreover, when ascarids become disturbed, due either to conditions produced by themselves or to secondary intestinal upsets as, for example, dietary indiscretions, they may be vomited and may be discharged through the nares or may be passed in the stool. At times they produce serious pathology. They may block the common duct and even penetrate into the substance of the liver and produce liver abscess. They may block the appendiceal lumen and initiate an acute appendicitis. They may perforate the intestinal wall and cause peritonitis. They may even migrate up to the pleural cavity and produce a condition suggesting empyema. Authentic records of such wanderings of this worm are fairly common in contemporary medical literature. More usually, perhaps, a mass of these worms becomes hopelessly entangled in the small bowel and produces acute ileus, requiring immediate surgical intervention. Finally, the by-products of dead worms in the intestine may produce grave systemic toxemia.

In children in endemic foci, particularly in Ascaris households or environments, the clinical picture is frequently complicated by continuous exposure to infestation and, therefore, consists of both pulmonary and intestinal ascariasis at one and the same time. Diagnosis of the mature worms is based on recovery of the eggs in the stools. Since both infertile and fertilized eggs may be discharged, both types must be identified and differentiated from undigested vegetable cells. The Ascaris pneumonitis can only be diagnosed on clinical and epidemiologic grounds, together with a history of ascariasis in the patient or in the patient's family.

In considering therapeusis in ascariasis, it must first be emphasized that in cases of acute ileus, with Ascaris eggs in the stools, purgatives and specific chemotherapeutics should never be administered; surgical removal is the only known safe procedure. In treating the infestation many physicians still use santonin, which is both toxic and relatively inefficient. Some use ascaridol (or oil of chenopodium), which is efficient but very toxic and dangerous except under strict supervision of hospitalized cases. In my opinion the drug of choice is hexylresorcinol crystoids in hard gelatin capsules. When given according to directions it is both safe and highly efficient.[20] For children under school age two capsules (0.4 gm.) are sufficient. For children from six to ten years old 0.6 to 0.8 gm. is recommended, and for those over ten years the adult dosage of 1.0 gm. is indicated. The entire course of treatment is given at one time, preferably in the morning on an empty stomach, and food is withheld for five hours, care being taken that the capsules are swallowed without being chewed up. For ascariasis it is desirable to follow the drug in about two hours with a saline purgative, in order to prevent dying worms from disintegrating within the bowel and their toxic by-products from being absorbed. At least 90 per cent of the worms should be removed with one course of treatment, but larvae in transit through the lungs are not affected and must be attacked chemotherapeutically after they have arrived in the intestine.

It is evident from this survey of ascariasis that specific chemotherapeusis is practical for individual cases, but is not permanently valuable when children are subject

to constant reinfestation. It is equally evident that therapeusis per se will not prevent reinfestation. This is a problem of family hygiene, particularly involving the mother and the small children. The common offender is the small child who defecates in a moist shady site in the dooryard, under the gallery, or even in the house.[16] Another source of infestation is the unsanitary privy in the country, where feces is allowed to overflow into the garden or onto the garden path. Still another source is the washings from the night jar which the mother may throw out in the yard. All such types of contamination constitute Ascaris "seed" for the environment, where the small child of the family or of the neighbor's family exposes itself and acquires the infestation. Constant efforts of the physician, working with an efficient visiting nurse or school nurse, can do much to reduce these hotbeds of infestation and eventually reduce the thankless task of continual treatment of the Ascaris child who is constantly becoming reinfested.

2. *Hookworm Disease.*—Hookworm disease, as it has existed in the southern United States for more than a century, is an intestinal infestation produced by the presence in the small bowel of the round worm, *Necator americanus.* These small worms live attached by their buccal capsule to the epithelium of the intestinal wall, where they suck on the villi and produce open ulcers. The females lay thin-shelled grayish hyaline colored oval eggs which are discharged in the stool in an early stage of embryonation. When such eggs are deposited on moist shaded sandy loam, they complete their development and hatch, the emerging larvae feed ravenously on organic débris in the soil, molt, feed again and then become transformed into infestive-stage larvae, which, on contact with exposed skin, penetrate down to the peripheral venules and are then carried in the blood stream through the right heart to the lung. They break out of the pulmonary capillaries, pass up the respiratory tree, over the epiglottis and are swallowed. On arrival in the small intestine they develop a mouth capsule, become attached to the wall, and rapidly grow into adult worms. The complete incubation period requires about five weeks.

The picture of hookworm disease in children in the South twenty-five years ago was one of profound malaise, with a marked anemia, emaciation, dry skin and hair, protuberant abdomen, abnormal hunger pains, geophagia, disturbed digestion, delayed physical and sexual growth, and intellectual stagnation. Except in isolated communities such advanced stages of the disease are less common today, although each year several such cases may be diagnosed and treated in city clinics, while county health officers have more common contact with them. Therapeusis and community- or family-hygiene have reduced both the incidence and intensity of hookworm infestation in the southern United States to a fraction of the previous figures, as Keller[21] has so well demonstrated for Tennessee. Yet until recently we had little or no proof of the actual mechanism whereby the hookworm produced the syndrome of the disease. Opinion previously favored the view that toxic by-products of the worms, when absorbed into the system, were primarily responsible for the disease. Both experimental and clinical evidence[22, 23] now indicate clearly that the anemia is essentially a microcytic hypochromic type, caused by the mechanical loss of blood from the intestinal wall, pumped out continuously by the worms through their bodies, and that this loss of blood eventually produces sufficient drain on the erythropoietic system, particularly in the poorly nourished child, to account for all of the complicating symptoms. It has also been demonstrated[23] that patients gravely ill with hookworm disease may be transformed into normal human beings by a balanced diet to which iron or liver and iron have been added, even without removal of the worms by specific therapeusis. While this is a dramatic demonstration, in practice these erythropoietic stimulants, at times supplemented by blood transfusion, should be used in building up the body preparatory to the administration of specific therapeutics to remove the worms.

Although the experienced physician will probably recognize his severe hookworm cases by physical examination, the milder cases can be diagnosed only by fecal examination. There are refined technics of egg counting for estimating the number of worms present, but these need not be employed for successful routine work. In my own experience I have found that unconcentrated feces provides a better criterion for the intensity of infestation than do concentration technics such as centrifugation and brine floatation. If no eggs are detected in three 40 by 20 mm. unconcentrated films of freshly passed feces, the infestation is so light as to be clinically unimportant. Except to the experienced laboratory worker concentration is likely to enrich the yield so as to overemphasize the clinical importance of the case. Furthermore, I do not believe that it is necessary for the physician to "deliver" the very last hookworm in order to discharge his professional service satisfactorily. It may be remembered that in freshly passed stools only hookworm eggs are usually seen, although larvae may hatch in feces left in a warm room overnight. Such larvae must be differentiated from those of Strongyloides, which produces different symptoms and requires a different therapeutic procedure. In recently infested hookworm cases, as well as in older ones, the feces may have a tarry consistency, due to the open hemorrhages produced by the worms in the small intestine.

Therapeusis in hookworm infestation has been radically modified within the past two decades. Chloroform and thymol were first replaced by oil of chenopodium, which in turn gave way to carbon tetrachloride. While both of these latter drugs have high anthelmintic properties, they are very toxic and are frequently contraindicated. Equally efficient and much less toxic is tetrachlorethylene. For each of these drugs 3 minims per year of age should not be exceeded. Their administration should be preceded the night before by saline purgation, preferably with Glauber's salts. The drug should be given on an empty stomach in the morning and followed two hours later by another saline purgation. Oil purgatives are contraindicated. Where the child is suffering from hookworm or nutritional anemia, a week's preparation with liver and iron may well precede specific therapeusis. In delicate children hexylresorcinol crystoids (as recommended for ascariasis) may be substituted, although the efficiency of this drug in hookworm eradication is only about 75 per cent. However, its administration may be repeated two or three times if necessary without harmful effects.

Hookworm disease is much less common in the small child than is ascariasis. It usually reaches its maximum incidence in children from eight to fourteen years of age. Unlike ascariasis it is not a problem of the dooryard, and wherever sanitary toilets or privies have been erected and properly used, together with anthelmintic treatment, the disease has been satisfactorily diminished or eradicated.

3. *Oxyuriasis.*—This disease is produced by the pinworm or seatworm, *Enterobius vermicularis.* The young males and females live attached to the wall of the lower levels of the ileum. Gravid females become free and migrate through the bowel, frequently wandering out the anus at night and crawling on the perianal and perineal skin, where they set up an insufferable pruritus. In children this usually occurs after the child has been put to bed. Eggs are not commonly laid within the bowel, but are set free outside the anus. They are usually fully embryonated and get on the fingers of the child in scratching the irritated skin. They may lodge under the finger nails or may be immediately carried to the mouth and, hatching in the small intestine, develop directly into adult worms without the necessity of migration to the lungs.

Aside from the pruritus and dermatitis produced in the perianal and perineal regions, the female worms may migrate up the genital tract of girls and reach the peritoneal cavity. Frequently infestation causes nervousness, insomnia, loss of appetite, hysteria, and even epilepsy, which disappear after removal of the worms. If eggs

are present in the stool, their identification is easily made. Yet I doubt if such eggs are found in more than 5 per cent of all infested cases. Examination of swabbings from the perineum or dirt scraped from under the finger nails is at times helpful in recovery of these eggs. However, in cases with seatworm infection, specific diagnosis is more readily made by having the mother bring one or more of the worms which she has removed from the anal region of the child and has preserved in alcohol to prevent drying.

Probably no infestation has been subject to so many grandmother's remedies as has this one. By and large practically all of them are unsatisfactory. The most successful therapeutic in my experience is hexylresorcinol crystoids by mouth (as recommended for ascariasis) to remove the attached worms in the ileum, supplemented by a retention enema to remove the migratory females (1:1,000 alkaline solution of hexylresorcinol, S.T. 37, introduced into the cecum after an ordinary tepid water enema has removed the feces from the large bowel). Chiodo[24] claims to have cured children of oxyuriasis with chiniofon, administering 0.25 gm. thrice daily by mouth supplemented by a 1 per cent solution of the drug introduced into the rectum.

Oxyuriasis is much more common in children than it is in adults. By nature of its direct transmission to the mouth from soiled bed linen and sleeping garments it tends to be familial and institutional in its distribution. In addition to specific therapeusis, the finger nails of infested children should be trimmed as short as possible, the children should be provided with closed sleeping garments so that their fingers will not come in direct contact with the itching areas, and they should be taught as soon as possible the dangers of putting their fingers in their mouths and the need for thoroughly scrubbing their hands, particularly before meals. Yet with all of these hygienic precepts thoroughly carried out (a Utopian dream!), infestation may persist, due to internal reinfestation. These cases demand repeated treatment, with success eventually possible.

4. *Trichinosis.*—This disease is produced by the "trichina" worm, *Trichinella spiralis.* It is usually acquired by consumption of raw or underdone pork, commonly in the form of country summer sausage or Italian style hams. Relatively uncommon in the South, this infestation is most frequently seen in New York, the New England states, St. Louis, Minnesota, and California. As far as I am aware, there are no available data showing the age incidence of trichinosis, although children are undoubtedly susceptible as are adults. Individual cases of infested children are on record, but usually the disease is contracted in family or picnic groups, where all of the individuals partook of the same infested meat. In infested children, however, the prognosis is usually better than in adults.[25] Peptic digest methods for isolating and concentrating the larvae from diaphragm at autopsy[26] indicate that there are undoubtedly many cases which were never diagnosed during life.[27]

The larval "trichina" worms are encysted in the lean pork meat. On ingestion and passage into the duodenum, the larvae excyst, invade the mucosa of the duodenum and jejunum and within a week develop into adult males and females. The viviparous females then begin to discharge their progeny into the intestinal wall. Most of these larvae get into the mesenteric lymphatics and venules and are carried to striped muscles where adventitious encapsulation takes place. This continues over a period of about six weeks.

During excystation and invasion of the intestinal wall, the symptoms resemble those of acute food poisoning. During migration of the larval progeny through the body excruciating myositis, severe rheumatic pains, and toxic edema, accompanied by hyperpyrexia, are the cardinal symptoms. A high eosinophilia is almost always characteristic of this stage. Its absence during the acute stage suggests a fatal termination.[28] Later, toxic symptoms, grave or less severe, with myocarditis, and at times encephalitis or meningitis, appear. The patient may succumb in the

early part of the third period, or may survive with a short or long convalescence. In endemic foci like St. Louis, where microscopic section of the diaphragm in routine autopsies shows a 25 per cent infestation of the population,[29] deaths are relatively few as a direct result of the disease.

Diagnosis is suggested by the history of food poisoning, rheumatic pains, and toxemia following consumption of raw or rare pork. High eosinophilia is suggestive of this disease. During the period of migration, the larvae may be recovered from acidulated blood which has been centrifuged and at times from the feces. Less commonly they have been obtained from spinal fluid, mother's milk, and mammary glands. Later, after encystation has occurred only biopsy specimens, usually taken from deltoid muscle, will provide a specific diagnosis. There is no known specific chemotherapeutic for this infestation, although human convalescent serum may be found effective.[30] Symptomatic treatment is always indicated. The bowels should be kept alkaline and open. Sedatives should be given to relieve the distressing myositis. Supportive treatment for the heart, lungs, and kidneys should be administered.

Prevention consists in the thorough cooking of all pork meat. Light infestations probably confer considerable immunity to subsequent exposures.

5. *Tapeworm Infestations.*—Under this category belong the beef tapeworm *(Taenia saginata)*, the pork tapeworm *(Taenia solium)*, the broad fish tapeworm *(Diphyllobothrium latum)*, the dwarf tapeworm *(Hymenolepis nana)*, the rat tapeworm *(Hymenolepis diminuta)*, the dog tapeworm *(Dipylidium caninum)* and others of less common occurrence in man. All of these worms live in the small bowel, with their "heads" attached to the wall. Each tapeworm (i.e., strobila) consists of a "head," a "neck" and a series of "segments" (proglottids), which begin with very immature units proliferated from the neck region and become successively more mature and finally gravid as they assume a distal position in the chain. Each proglottid is a complete, sexually independent hermaphrodite. The "neck" is the region of growth; as long as the "head" remains attached to the patient's intestinal wall, it is capable of proliferating an entire new strobila. The relative incidence of these several tapeworms varies considerably throughout the United States. *Taenia solium* may be conservatively estimated as being not more than one-tenth as common as *T. saginata*. In New Orleans the ratio is approximately 25 to 1, with cases of *T. saginata* recorded for children of four, eight, nine, ten, and twelve years during the past five years. Levin and Pilot[31] reported this worm in a two-month-old infant, who became infested from improperly prepared beef juice. In children of Scandinavian and Jewish parentage in the North and in New York City the broad fish tapeworm is most commonly found. *Dipylidium canium* is almost exclusively a childhood infestation, acquired from accidentally ingesting infested dog or cat fleas. Cases are relatively rare in this country. The rat tapeworm *(H. diminuta)* has been found in children in Texas, Georgia, Arkansas, California, the District of Columbia, Virginia, Indiana, Minnesota, Nebraska, North Carolina, and Tennessee.[32] An unreported case is also known for Louisiana.

The most common tapeworm in children is *Hymenolepis nana*. It is present throughout the South and is encountered from time to time throughout the North. In statewide surveys, such as that conducted in Tennessee,[33] it may reach a maximum incidence of 3.6 per cent in the five- to nine-year-old group, with 2 per cent in the one- to four-year-old group, while in Mississippi[34] the figures were found to be 0.6 and 0.5 per cent, respectively. In New Orleans clinics the incidence is considerably lower.[5] In children's homes, however, the incidence usually is high, as for example, 32.6 per cent in a Texas orphanage[35] and 9.25 per cent in New Orleans institutions.[36] After fifteen years of age the incidence rapidly declines, but cases have been diagnosed as late as fifty-eight years of age. In a given population the incidence apparently remains about stationary over many years.[34] The relatively

high incidence of infestation with the dwarf tapeworm is due to the ease with which it is propagated, without the need of an intermediate host. This accounts for the large percentage of cases in children's asylums and in large families where personal hygiene is on a low level.

In all of the tapeworms considered here, with the exception of *D. latum*, the egg contains a fully developed characteristically six-hooked embryo at the time it is discharged in the stool. It is therefore ready to be taken into the next host to continue its life cycle. For *Taenia saginata* and *T. solium*, the mature larval stages infestative for man are found respectively in "measly" beef and pork muscle, which, when consumed raw or rare, produces human infestation. For the rat tapeworm and the dog tapeworm, the larval hosts are certain insects such as fleas, which, when accidentally swallowed, cause infestation. The broad fish tapeworm occurs in its infestive stage in fish flesh. *Hymenolepis nana* requires no larval host; the egg passed in the stool is immediately capable of setting up human infestation when ingested by man.

All of these tapeworms probably produce some degree of toxemia in the host, particularly in the small child. The clinical manifestations usually include disturbed digestion, with abnormal hunger pains, particularly at night; diarrhea; loss of weight; insomnia; anemia; nervous symptoms, with loss of reflexes and occasionally epilepsy. The degree and type of the syndrome vary widely with each particular case.

Diagnosis consists in finding the eggs and at times the proglottids of these worms in the stools of the patient. From ancient times various anthelmintics have been used in the treatment of tapeworm infections, including quassia, pumpkin seed, pelletierin, etc. One drug alone has stood the test of time, namely the oleoresin of male fern *(filix-mas)*. For its administration the patient should receive saline purgation the night before treatment. In the morning, while in bed and without breakfast, the patient should receive 2 to 3 minims of the pure drug per year of age. This may be administered (1) in a hard gelatin capsule, (2) with sugar on a teaspoon, or (3) (preferably in children) through a duodenal tube.[37] Two hours later a follow-up saline purgative should be given. Best results are obtained if the patient remains in bed to minimize nausea and dizziness and takes no food until a copious bowel movement has been obtained. All stools should be saved for forty-eight hours following anthelmintic medication and examined in search for the "heads" of the worms. No treatment is successful unless the "heads" are evacuated.

In tapeworm infestations prevention depends on the source of the infestive material. Thorough cooking of suspected meats, such as beef, pork or fish, and care not to contaminate the mouth or hands constitute important prophylactic procedures.

### *Conclusions*

Only the more important parasitic infestations of the gastrointestinal tract of man have been considered. Some of these like giardiasis, ascariasis, and dwarf tapeworm infestation are peculiarly childhood diseases, due primarily to the simple life cycles of the parasites which are accommodated to the environmental conditions, but also possibly less common in adults as a result of the development of resistance to the infestation. They may be looked for as common infestations of the one- to five-year-old group. Other infestations, such as amebiasis, hookworm disease, oxyuriasis, and trichinosis, are clinically as important in the young child as in the adult, although their incidence is lower in children. They may be expected to occur more frequently in children from five to fifteen years old. It is, therefore, a particular duty of the pediatrician to be "parasite-conscious" when examining his patient, to appreciate the potential seriousness of such infestations and to utilize every possible method not only to treat the individual case but to instruct his patients in ways to prevent reinfestation.

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DISCUSSION

DR. CALEB O. TERRELL (FORT WORTH, TEXAS).—Is there glycerin in S. T. 37?

DR. H. H. PERLMAN (PHILADELPHIA, PA.).—Yes, S. T. 37 does contain glycerin.

DR. DWYER (KANSAS CITY, MO.).—Isn't S. T. 37 very expensive?

DR. E. D. ANDERSON (MINNEAPOLIS, MINN.).—Have you much difficulty in getting small children to swallow the crystoids?

DR. PERLMAN.—Is there not danger of stomatitis from chewing the crystoids?

CHAIRMAN FAUST.—We have no trouble from the chewing of the present-day hard gelatin-covered crystoids.

DR. TERRELL.—Is garlic in extract or oil effective in the treatment of pinworms?

CHAIRMAN FAUST.—It is said to be and is used by the Italians a great deal, but I do not know how effective it is.

DR. P. E. LUECKE (DALLAS, TEXAS).—How about wheat germ in oil, giving 1 or 2 capsules a day for from ten to fourteen days?

CHAIRMAN FAUST.—I do not know.

DR. ROLAND STAHR (FORT DODGE, IOWA).—How often can you have the organism present in the intestinal tract without symptoms?

CHAIRMAN FAUST.—If there is a heavy infestation, I think you will be likely to have symptoms of some kind.

DR. TERRELL.—Is the local application of ammoniated mercury ointment around the rectum important in the treatment of pinworms?

CHAIRMAN FAUST.—Because of the excessive itching, there is likely to be scratching, and, because of this, secondary infestation often occurs; therefore ammoniated mercury is important as a palliative for the pruritus, but it does not kill the worm.

DR. C. E. BRADLEY (TULSA, OKLA.).—Oxyuris is the most prevalent parasitic infestation in our district. Hexylresorcinol crystoids are used and have given good results. Our real problem is to get the child entirely rid of infestation. We can get immediate relief, but then we often have frequent recurrences. Most of my cases are diagnosed by routine blood examinations which show high eosinophilia, and then we get eggs of the worm when repeated stool examinations are made.

## Diagnosis of Intestinal Parasitic Infestations

**H. L. Dwyer, M.D.**

The management of intestinal parasitic infestations in children in the private practice of the average physician is just about where it was a quarter of a century ago. Although much progress has been made in this field by public health workers and parasitologists, the accurate methods of diagnosis, chemotherapy, and the studies on the life cycle of parasites have not found their way into the office practice of the great majority of physicians. A diagnosis of worms is made oftentimes from a history of vague subjective symptoms, a procedure that is notoriously inaccurate. Consequently, the therapy of intestinal parasitism is for the most part empiric, consisting as it does of prescribing one of the proprietary vermifuges without having first determined the presence of parasites by stool examinations.

Fortunately, the empiric treatment of intestinal parasitism usually does no harm. Serious and vigorous treatment that is really effective has not been without danger in the past, even in the hands of those skilled in parasitology. The older forms of treatment especially, in which a long period of purgation and starvation was the rule, both before and after the administration of a drug, itself more or less toxic, was sufficient to tax the patient seriously. A well-known internist has stated that the separation of a man from his tapeworm is attended by as much trouble and the same hazard as the birth of a baby.

Suffice it to say, that treatment should not be undertaken until the presence of parasites is established. We should determine whether the patient harbors more than one species of parasites, whether there is a heavy or a light infestation, in other words, how much he is in need of treatment, and finally, how much the general health has been impaired as a result of the parasites.

We should deal as far as possible in specific treatment, bearing in mind that a certain anthelmintic may remove nearly 100 per cent of one type of parasite and be totally ineffective against another. Specific therapy requires accurate diagnosis.

Certain clinical symptoms commonly associated with the presence of worms, although of little importance in diagnosis, should prompt the physician to examine the stool microscopically.

The most common symptoms attributed to worms are hunger, pallor, enlarged abdomen, grinding the teeth during sleep, picking the nose, capricious appetite, loss of appetite, abdominal pain, malnutrition, fatigue, mental retardation, and rectal itching. The physician hears these symptoms described so many times by parents, in ascribing to worms—symptoms that are in fact due to other causes—that he finally comes to the point where he is inclined to discount such symptoms. Nevertheless, every one of them may result from intestinal parasites.

It is surprising that roundworm and hookworm infestations do not cause more symptoms than they actually do. The larvae of these parasites spend some of their time circulating in the blood stream, rupturing the capillaries and alveoli in the lung, and migrating around the bronchioles. Worms have been found migrating into all the ducts opening into the bowel, passing through the bile duct into the liver, through the pancreatic duct into the pancreas, completely occluding the lumen of the appendix, perforating the bowel to enter the peritoneal cavity, and even into the pleural cavity. They may pass from the pharynx down into the trachea to obstruct the air passages. They may occur in such numbers in the bowel as to produce obstruction. Some species burrow into the mucosa of the bowel to live on the blood, or to produce ulcerations and cause long-continued loss of blood. Fortunately, all of these more serious complications occur only in heavy infestations and are relatively uncommon. One can see, however, that parasites are capable of producing a great variety of bizarre symptoms in the child.

We are concerned with making a diagnosis long before such symptoms are present and before there are serious inroads on the child's health. Therefore, from a practical standpoint, I think it is safe to say that, with the one possible exception of anal pruritus, the clinical symptoms of intestinal worms are of little value. Itching at the anus is a very good sign of pinworm infestation.

Intestinal parasitic infestations can be determined by the presence of their ova in the stools in the cases of the roundworm, hookworm, pinworm, whipworm and tapeworm. In the large tapeworms, *T. saginata* and *T. solium*, segments of the adult worm may also be found. Infestation with *Strongyloides stercoralis* is detected by the presence of larvae in the fresh stool. Any of these parasites, with the exception of the hookworm, may be found in all parts of the country, although the incidence varies greatly. A knowledge of the prevalence of parasites in our respective localities will be of some help in finding them.

In the examination of the stool specimen, which is usually collected in a glass jar, one should inspect it carefully through the glass for adult worms. A roundworm or segments of tapeworm may be found and the very small pinworm may adhere to the side of the jar. A small quantity of feces is then mixed with a little water and spread on a microscopic slide in a film of such density that ordinary print will be discernible through it. It is necessary that the stool be a fresh specimen and kept warm if one is to detect motile amebas.

This simple smear may be all that is required for the Ascaris and hookworm, because of the enormous number of eggs they pass. After three or four such specimens fail to show parasites, a more concentrated specimen must be examined. There are two methods of concentrating the ova, the brine flotation method—the easier and more adaptable to routine office work—and the centrifuge method, which may be carried out as follows:

*Brine Flotation Method.*—About one-half teaspoonful (2 gm.) of feces is mixed with 1 ounce (30 c.c.) of a saturated salt solution. After it stands from fifteen to twenty minutes the top, which is likely to contain the eggs, is carefully transferred

to a glass slide. This is done by touching lightly the mouth of an inverted test tube to the surface of the solution and transferring it to the slide. Except for certain tapeworm eggs which do not float, this is a reliable method of examination.

*Centrifuge Method.*—In the centrifuge method of concentrating ova, an emulsion of stool and water (or water from the washings of a formed stool in the case of *Enterobius vermicularis*) is strained through two layers of gauze into a test tube and centrifuged for a few seconds only. The supernatant fluid is carefully poured off. This fluid contains principally bacteria and lighter particles. The sediment, which presumably contains the worm eggs and heavier particles, minus the bacteria in the supernatant fluid, is covered with tap water, thoroughly shaken and centrifuged again for a few seconds. After another washing of this sediment, nearly all the supernatant fluid is poured off and it is spread on the slide in a thin film. A careful search of two or three such preparations will usually detect ova if they are present.

In the case of pinworms the examination of smears made from anal scrapings may be of more value than those made from the stool. When they are made from the stool specimen, they should be obtained from the first of the passage and only from the formed stool. This should not be emulsified. Water from the washing of the stool is more likely to contain the ova.

The accuracy of the centrifuge method depends to some extent upon the speed and the length of time the specimen is centrifuged. About 8 to 10 seconds in a good high-powered centrifuge is desired. With a small centrifuge a longer time is needed.

Amebic dysentery is characterized by blood and mucus in stools, with considerable tenesmus. The diagnosis is as a rule not difficult if a warm, fresh stool is examined. The amebas are prone to come down in the stools in showers; the following stools may contain very few. A few flecks of blood and mucus spread on a warmed slide will usually disclose motile amebas.

I do not know how to distinguish between the encysted *Endameba histolytica* in formed stools, the infectious form of the parasite, and other amebas, which are nonpathogenic. In fresh specimens pathogenic amebas phagocytose blood cells, others do not.

The flagellates, Giardia and Trichomonas, are not infrequently found in this locality. *Trichomonas vaginalis* is occasionally found in the urine. I have never observed any symptoms from these infestations and have found them only in the course of routine examinations.

The large roundworm, *Ascaris lumbicoides,* is one of the most common parasites of children. It is 6 to 10 inches long and superficially resembles the ordinary earthworm. The physician's attention is usually directed to Ascaris infestation when the child passes the worm or when it is vomited. There are no definite symptoms in the great majority of cases. When numerous they are capable of producing abdominal pain, digestive disturbances, anemia, and nervous disorders, such as disturbed sleep, grinding of the teeth at night, night terrors, and convulsions. In those rare instances when they wander from the bowel, they may cause any of the more severe disturbances mentioned above. Heavy infestations have been known to cause chronic bronchitis, and enlargement of the hilar lymph nodes have been found in comparing x-ray shadows of heavily infested children with normal children. This comes from migration of the larvae into the small bronchi and probably also from an associated bacterial invasion of these structures.

The diagnosis of Ascaris infestation is not difficult. A simple smear made by mixing a small quantity of feces with water on a glass slide may disclose ova because Ascaris passes an enormous number of eggs. If they are not readily found with the simple smear, the brine flotation method should be tried.

The hookworm, *Necator americanus,* is confined to the southern states, and the infestation is acquired in the rural districts. The larvae develop from the eggs passed in the warm soil and penetrate the skin of the feet. Excoriations between the toes

produce a characteristic lesion known as "ground itch." The larvae are carried by way of the lymphatics and veins to the right side of the heart, thence to the lungs, where they gain access to the pharynx and are swallowed. In the intestinal tract they do not multiply; the number is increased by repeated infestations.

Hookworm infestation does not mean hookworm disease. A light infestation produces no symptoms. A heavy infestation may result in the most severe symptoms of any intestinal parasitic infestation. The female worm is about one-half inch in length and fastens itself in the intestinal wall where it sucks blood. Severe grades of anemia and malnutrition, general apathy, malaise, and mental retardation are well-known in hookworm disease.

The microscopic detection of hookworm ova is not difficult. The first-stage hatched larvae of the parasite resemble the *Strongyloides stercoralis* larvae. In a freshly passed stool of the hookworm patient, only the ova are present, while in Strongyloides infestation the very active larvae are found on the microscopic slide. The life cycle of the Strongyloides is in many respects similar to that of Necator.

Infestations with the pinworm, *Enterobius vermicularis,* are characterized by pruritus ani. This, usually discovered by the mother, is probably the most common and widespread intestinal parasitic infestation. They have been known to cause balanitis and vaginitis when they wander from the anus. The other gastrointestinal and nervous symptoms so frequently attributed to parasites, such as mucous colitis and disturbed sleep, have resulted from pinworm infestation. By far the most constant and valuable diagnostic sign is the rectal itching, especially at night.

The diagnosis is made by finding the adult worm in the folds of the anus. The female worm, twice as large as the male, measures ¼ to ½ inch in length. A magnifying glass with a good light should be used in the examination.

The life cycle of the pinworm is the simplest of all the intestinal parasites. The female worm does not regularly pass eggs but stores them in the uterus as she passes out into the anal region. The eggs escape by desiccation of the worm, or from the scratching of the patient and are carried to the mouth to be swallowed.

In stool examinations it is best to obtain a washing of the formed stool, preferably the first part passed that has been longer in contact with the rectum. A very small amount of water for this purpose, placed on a microscopic slide may show ova when adult worms cannot be found adhering to the formed stool or on the side walls of the glass jar containing the specimen. Examination of anal scrapings obtained with the end of a moistened tongue depressor and transferred to the slide should always be attempted before examining the stool.

Trichinosis is more common than is generally supposed. Federal meat inspection does not include examination for this parasite. Recent surveys in the northern states disclose a human infestation rate of nearly 20 per cent, and in some localities dogs and cats are at times infested. The characteristic symptoms of toxemia come only when the encysted larvae reach the muscles, producing muscle cramps, fever, and a marked eosinophilia. The diagnosis is made by biopsy. Evidently it requires a rather heavy infestation to cause symptoms because in most of those cases showing larvae in the diaphragm at autopsy no antemortem symptoms were present.

*Taenia solium, T. saginata,* and *Trichinella spiralis* are transmitted to man only through insufficiently cooked meat. *T. solium* passes part of its life cycle in the hog. It is still more or less cosmopolitan in its distribution, particularly among the foreign-born of our large cities, where minced or semi-raw pork is eaten. The cystic stage of this parasite, *Cysticercus cellulosae,* is rarely found by the federal meat inspectors at the Kansas City abattoirs, although it is occasionally found in Denver (about 75 times last year). The hogs become infested from the Mexican laborers in the beet fields. The cysts of *T. saginata, Cysticercus bovis* are occasionally found in the abattoirs in this region although not nearly as frequently as they were ten or fifteen years ago.

The dwarf tapeworm, *Hymenolepis nana*, is by far the most common tapeworm of children. This is probably due to the fact that it requires no intermediate host, the eggs are ingested directly. Children in institutions may transfer the eggs to one another from hand to mouth. The worm is only 3 to 4 inches long, but many hundreds may be present in the intestine. They do not pass nearly as many eggs as roundworms; consequently the more concentrated film from the stool is required—either the brine flotation preparation or that obtained by a short period of centrifuging.

The large tapeworms, *T. saginata* and *T. solium*, produce abdominal pains, especially at night, disturbed sleep, grinding of the teeth, and other nervous symptoms, and they may seriously affect the nutrition. The diagnosis is most often made by finding a large part of the worm squirming about in the stool. These worms are flat and segmented, and each day or two a few of the last segments break away to pass out of the bowel.

The beef and pork tapeworms do not pass their eggs regularly. Only when the segments become broken or digested in the bowel, freeing the ova, will they be found in the stool. It may require a saline purgative to bring away portions of the adult worm for diagnosis. The eggs of these parasites are porous and do not float on the surface of a salt solution, therefore, the rapid and short period of centrifuging is needed for the stool specimen.

### Chemotherapy in Intestinal Parasitic Infestation

**Horton Casparis, M.D.**

In the case of amebic dysentery or the carrier state, we have used carbarsone, two doses a day for ten days. It comes in 20-dose vials, enough for one course of treatment. This treatment has proved quite satisfactory. After ten days or two weeks a second course can be given if necessary.

We have found the most satisfactory drug for treatment of Ascaris infestation is hexylresorcinol crystoids. If one finds a case of intestinal obstruction due to Ascaris then surgery is resorted to rather than the usual form of treatment for parasites.

In the case of hookworm infestation the most satisfactory treatment in our experience is with tetrachlorethylene. If one finds hookworm and Ascaris in the same patient, the Ascaris should be treated first with hexylresorcinol crystoids since some of the drugs used for hookworm treatment are rather exciting to the Ascaris and may result in mechanical difficulties due to abnormal migration of the Ascaris.

Although the treatment for infestation with oxyuris or seatworms (i.e., *Enterobius vermicularis*) has been improved, it is still not entirely satisfactory. We use hexylresorcinol crystoids by mouth and employ coincidentally a 1:1,000 dilution of the same hexylresorcinol in the form of enemas, but I understand the powdered material is not on the market. Dr. Faust mentioned that hexylresorcinol in the form of S. T. 37 is rather satisfactory given as an enema in the same dilution as mentioned above. This of course is used along with the hexylresorcinol crystoids by mouth. Dr. Faust's statement that the cycle of these parasites can be completed in the intestinal tract explains some of our failures when we have taken every precaution to break the reinfestation cycle.

The treatment for tapeworms still offers a great deal of difficulty, but in our experience oleoresin of male fern is the most satisfactory drug and should be administered preferably through a duodenal tube to get the best results. We have been able to get the heads of worms using this method. Finding the head in the fecal material, of course, is difficult but extremely important.

#### DISCUSSION

DR. TERRELL.—How long would you give S. T. 37 retention enemas?

CHAIRMAN FAUST.—We wait one week after the first treatment and then if there are pinworms found we repeat, sometimes three or four times at weekly intervals.

DR. TERRELL.—How about quinine infusion?

CHAIRMAN FAUST.—I do not know.

DR. JOHN ZAHORSKY (ST. LOUIS, MO.).—I believe that infestation with Giardia is the next most common infestation to oxyuris. Not long ago I saw a baby with chronic diarrhea which I found did not improve with a dietary regime. I found that the stools were infested with Giardia. On treatment with bismuth subsalicylate the symptoms improved. Usually one cannot entirely get rid of the cysts. I had some twins under my care who showed very slow growth, frequent loose stools, and large abdomens. When treated with bismuth subsalicylate they improved definitely. However, after several years cysts are still found to be present. Apparently, over a period of years some adjustment takes place between the parasites and the host and the child will do well, even though not free of the infestation. Microscopic examination of the stool is made and the cysts are found, giving the diagnosis.

DR. STAHR.—In what dose is bismuth subsalicylate given?

DR. ZAHORSKY.—Five grains, three times a day.

DR. PERLMAN.—What is the effect of Glauber's salt?

CHAIRMAN FAUST.—Purely as a lavage—not a cure.

DR. ZAHORSKY.—We use hypertonic solution of salt as an enema for pinworms. It is effective in the relief of this condition.

CHAIRMAN FAUST.— It is not a specific.

DR. STAHR.—Is there any foundation for the claims for chrysamine in strongyloidiasis?

CHAIRMAN FAUST.—Chrysamine is not as good as gentian violet.

DR. ZAHORSKY.—Anthelmintic candy is more effective in expelling tapeworm than male fern.

DR. STAHR.—I had two children with pinworms under my care. Each had a bark which was neither a cough nor a hiccough and which went on for months. Under the fluoroscope they showed a diaphragmatic spasm. When treated with hexylresorcinol, this stopped immediately.

CHAIRMAN FAUST.—I do not know if the bark could be due to pinworm infestation, but I think it barely possible from my knowledge of other larvae.

DR. ZAHORSKY.—We pediatricians have overlooked the symptomatology of parasitic infestations. We should inquire into the history of the cough. In animals a dry hacking cough is a symptom of intestinal worms.

DR. A. F. HARTMANN (ST. LOUIS, MO.).—I had a patient under my care on whom a diagnosis of roundworm infestation was made. This was a nine-year-old diabetic child, in a good state of nutrition and well adjusted with diet and insulin as far as the diabetes was concerned. She was given a mixture of carbon tetrachloride, 2 parts, and oil of chenopodium, 1 part, in a dose of 3 minims per year of age, making a total of 27 minims, followed in two hours by magnesium sulphate. About thirty-six hours later she became ill with what proved to be acute yellow

atrophy and died three days later. Postmortem examination confirmed the clinical diagnosis of acute yellow atrophy, showing an acute liver necrosis, acute enteritis with multiple small hemorrhages, and fatty degeneration of the renal epithelium. Large amounts of dextrose, calcium gluconate, and lactate—Ringer's solution—were used in the treatment after signs of the acute yellow atrophy had developed.

DR. BRADLEY.—Little has been said of the blood of a person infested with intestinal parasites. Do you not think there is almost universally severe anemia and eosinophilia present?

CHAIRMAN FAUST.—In the case of amebiasis there is usually no deviation in the blood picture unless there has been an extreme loss of blood, that is, mechanical loss from lesions. In helminthiasis one usually expects eosinophilia, but this is only a secondary effect of the infestation. If eosinophilia and leucocytosis are present, the prognosis is good. Blood findings are not necessarily consistent in any of the parasitic infestations except trichinosis, in which you do have a very high eosinophilia.

DR. OLIVER W. HILL (KNOXVILLE, TENN.).—I have found considerable infestation with Strongyloides in the southeastern part of Kentucky. We had one death that I am confident was due to Strongyloides. A postmortem examination showed a massive infestation of the intestinal canal. We have been able practically to eradicate this with gentian violet. I think I do not remember having enjoyed using any medication as much as gentian violet in treatment of these infested children.

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## MEETINGS OF NEW JERSEY MEMBERS OF THE AMERICAN ACADEMY OF PEDIATRICS

The annual meeting of the New Jersey Fellows of the Academy of Pediatrics was held at Atlantic City, June 3, 1936.

In the afternoon there was a symposium, "Methods to Increase Maternal Nursing of the Newborn," prepared by Dr. L. C. Rosenberg in the form of a panel discussion. Dr. F. W. Lathrop introduced the members of the panel, which consisted of four pediatrists and four obstetricians. The discussion was opened and led by Dr. Julius Levy. The members of the panel were Dr. Kenneth Blanchard, East Orange; Dr. Harrold A. Murray, Newark; Dr. E. G. Hummel, Camden; and Dr. Maurice Ripps, Elizabeth (pediatrists); Dr. Samuel Cosgrove, Jersey City; Dr. A. W. Bingham, E. Orange; Dr. A. B. Davis, Camden, and Dr. R. A. McKenzie, Asbury Park (obstetricians).

Following a dinner attended by about twenty of the Fellows from New Jersey, Dr. Stanley Nichols called the official meeting of the section to order. The purpose of the meeting was to acquaint the Fellows with the immediate program of the New Jersey section.

Dr. Nichols appointed a committee to draw up recommendations for the care and supervision of the newborn with the purpose of encouraging maternal nursing. The consensus of opinion at the afternoon symposium had been that it would be advantageous to publicize standards of care which the general practitioner might strive to emulate.

Dr. F. W. Lathrop was appointed reporter for the New Jersey section for the ensuing year.

The immediate program before the New Jersey section of the Academy of Pediatrics, as outlined by Dr. Nichols, consisted of the following objectives:

1. Public Health Hour. He emphasized the immunizations against diphtheria and smallpox, getting the patients under the personal care of a private physician. He suggested that it may be necessary to revert to health department immunization clinics for the indigents only.

2. He emphasized the preventive medicine viewpoint of the pediatrist and urged all pediatrists to make distinct efforts to be appointed to their county public health committees. In the discussion it was suggested that a letter be sent to each county secretary, giving a list of the Fellows and requesting that these men be put on the public health committee.

3. He urged postgraduate pediatric education for the benefit of the general practitioners, emphasizing preventive medical care.

4. He recommended group testing of high school students for tuberculosis as an advance toward the control of tuberculosis, keeping this work under the supervision and control of the medical profession.

5. He brought to the attention of the members child health under the Social Security Act, particularly the administration of the well-baby stations, insisting on procuring adequately trained and qualified physicians for these stations, free from political or partisan appointments.

*Panel discussion* on the question, Are the hospitals of the state encouraging or discouraging maternal nursing of the newborn?

Dr. F. W. Lathrop, Plainfield, chairman, introduced the four pediatricians and the four obstetricians and then presented Dr. Julius Levy, Newark, the discussion leader.

Dr. Levy stated that the purpose of this discussion is to consider the fact that a very large percentage of infants are being artificially fed in whole or in part by the end of the first month. Lack of pediatric supervision is demonstrated by the wide variety and bizarre types of formulas given the mothers on discharge from the hospitals. As illustration of the tendency toward bottle feedings, records of 1,365 women in Newark showed that of infants born at home, 84 per cent were entirely breast fed at the age of two weeks, while this was true of only 46 per cent of those born in hospitals. Since in many cities as high as 80 per cent of the total births are occurring in institutions, a definite consideration of the practices regarding early feeding in hospitals is desirable.

Dr. Kenneth Blanchard, East Orange, detailed the routine care at the Essex County Homeopathic and Orange Memorial Hospitals, where the nursery is in charge of obstetricians. He was impressed by the low percentage of mothers on the private service who were entirely nursing their babies on discharge. He quoted the late Stafford McLean to the effect that the physician is frequently responsible for the failure of nursing when he allows the mother to wean her baby without adequate justification for this step. Dr. Blanchard emphasized that slight temporary loss in weight should be disregarded. The tendency to resort immediately to complementary feeding results in a decrease in the infant's appetite, hence less vigorous nursing, and failure to empty the breasts thoroughly. Thus early complementary feeding hastens the ultimate failure of the breast supply.

Dr. Samuel Cosgrove, Jersey City, reported that at the Margaret Hague Maternity Hospital, 84 per cent of the babies were wholly breast fed at two weeks. He attributed these good results to intensive prenatal instruction pointing to the expectancy of successful nursing, care of the breasts and nipples before and after birth, constant selling the idea of breast milk to the mothers, and thorough emptying of the breasts, by mechanical breast pump if necessary. He believes that the universally less satisfactory results among private patients are due largely to the poor psychologic preparation of the mother and a lessened physical capacity for nursing among the well-to-do, less inclination to make social sacrifices, greater confidence in artificial feeding because of economic ability to meet the expense and to command competent pediatric assistance, greater susceptibility to psychologic influences, and temperamental rejection of the responsibility of the mother as the source of nutriment for the infant among some mothers.

Dr. Harrold A. Murray, Newark, reported that at the St. James Hospital in the past six months, since the formulation of definite rules to encourage breast feeding with the nursing under the care of pediatricians, the percentage of babies discharged entirely breast fed has increased from 50 to 70 per cent. He emphasizes the fact that no complementary feedings are used unless explicitly ordered, and then only with definite contraindications to nursing and not in the first few days of life. Weak tea or 5 per cent glucose is used before the milk comes in. He feels that prenatal care, especially controlling the psychic factor, is of great importance.

Dr. A. W. Bingham, East Orange, detailed the routine care at the Orange Memorial Hospital. He believes the mothers of partially breast-fed babies must be persuaded to continue nursing for five or six months with the complementary feedings to help out their own inadequate supply.

Dr. E. G. Hummel, Camden, reviewed the theoretical considerations underlying the use of hydrating solutions of beta-lactose and sodium citrate for the newborn as follows:

1. The need of fluid combined with a hydrating agent to compensate for the dehydration following birth.

2. The need of the newborn for food, particularly sugar, during the prelacteal period, to prevent acidosis.

3. The opinion of authorities to the effect that foreign proteids given during the prelacteal period are useless if not dangerous.

4. The desirability of establishing an intestinal condition which later will not be abruptly changed whether the infant proceeds on the breast or is artificially fed.

He cited a study in which a group of hospital infants given beta-lactose and breast milk showed a decidedly better gain in weight than a control group receiving only water and breast milk.

He outlined the following schedule:

1. Putting baby to the breast every six hours after the first eight hours until the milk comes in, then every four hours.

2. Restriction of nursing to from three to five minutes until lactation is established.

3. Equating fluids to one-sixth of the body weight, daily.

4. Use of hydrating solution of water, beta-lactose, and sodium citrate during the inanition period. Infants under five pounds or showing weakness or starvation should have additional feeding.

5. Complementary feedings if the weight loss is over 8 ounces or if the infant shows starvation—acetone urine or starvation stools (persistent meconium).

6. Complete emptying of breasts.

7. Persistent encouragement of the mother.

Dr. Maurice Ripps, Elizabeth, gave a comparison of the methods and results at two hospitals. At one hospital only 31 per cent of the private patients were sent home on breast feeding, while at the other 78 per cent went home wholly breast fed. The important difference in the routine at the second hospital was a complete withdrawal of complementary feeding after the fourth day and insistence of the attendants on maternal nursing. He felt strongly that proper encouragement on the part of the attendants and their attitude toward the patients are far more important than the state of nutrition of the mother, and that the type of prelacteal feeding employed is not so vital as the number of days it is used.

Dr. A. B. Davis, Camden, outlined the care at the Cooper Hospital, and suggested that the nipples of the bottles should be small and difficult to nurse from, so that the infant will find the breast easier than the bottle.

Dr. R. A. McKenzie, Asbury Park, outlined the routine at Monmouth Memorial and Fitkin Hospitals. He emphasized prenatal care, with the prevention of anemia, adequate care of the nipples, and psychologic preparation of the mother, the frequent use of the breast pump to empty the breasts thoroughly, maintenance of body weight through prelacteal feeding of beta-lactose and sodium citrate, and skillful nursing supervision.

Dr. David Corn, Ridgewood Park, suggested that the state society send out authentic directions and advice on the problem of feeding normal newborn infants.

Dr. Levy questioned if nursing for three minutes at six-hour intervals develops the breasts properly.

Dr. Murray emphasized that a strong infant will traumatize delicate nipples if he nurses twenty minutes at a time the first few days of life. The baby does need extra fluid.

Dr. I. B. Rothstein compared 100 babies given water and glucose with 100 babies given stock formula in the prelacteal period, with a slight difference in favor of the glucose solution.

Dr. Chester Brown made a similar comparison of 100 babies on breast milk and water and 100 on breast milk plus stock formula, with the former gaining decidedly more in weight. He stated that a pediatrician in charge is more likely to keep the infants away from a stock formula and to be successful in keeping the baby on the breast.

Dr. L. C. Rosenberg said that whether or not the infant regains its birth weight by the time it is discharged from the hospital is of no serious concern. He also remarked that infants given complementary formulas are more likely to vomit.

Dr. Gibbs Chisholm reported unusual success with colored patients by insisting on breast feeding alone.

Dr. Levy advised elimination of stock formulas from hospital regime unless ordered by the attending physician, further education of the doctors, and more persistent encouragement of the mothers.

Dr. Ripps stressed the need of educating the general practitioner in regard to the importance of babies being breast fed. If no complementary feeding is given, the baby will take the breast better. If the baby goes home with complementary feeding, he will be weaned soon.

Dr. Lathrop proposed that the Academy establish a committee to formulate practices to be recommended to the practitioners of the state.

* * * * *

A dinner meeting of the New Jersey Fellows of the American Academy of Pediatrics was held Dec. 2, 1936, at Essex House, Newark.

Dr. Frederic Lathrop presented the resolutions on standard practices for increasing maternal nursing, which were accepted and will be mimeographed for distribution.

Dr. Stanley Nichols announced the death of Dr. Arthur Stern. Dr. Stern's death was the first since the organization of the New Jersey Branch of the American Academy of Pediatrics.

Dr. Nichols appointed Dr. Walter B. Stewart chairman of a committee to assist the state medical society public relations committee to secure speakers on child health.

Dr. Nichols turned the chair over to Dr. LeRoy A. Wilkes, who presided for the rest of the evening.

Dr. Thomas K. Lewis, of Camden, chairman of the state society subcommittee on medical practice, spoke on "The Future of Medical Practice."

Dr. Nichols was the first speaker on the subject, "The Opportunities and Responsibilities of the New Jersey Fellows in the American Academy of Pediatrics." Dr. Nichols stressed the fact that the office of every physician in New Jersey should be a health center for the practice of preventive medicine. The pediatrician is the one to lead in the development of the program, as 1937 is going to be a crucial year for the medical profession. A week ago the Social Security Board decided to study health insurance again. We hope the American Medical Association and the state medical societies will also join in this study and show the authorities that the medical profession is the most able group to provide medical service to the public and the way in which it is now being provided without insurance. We have found from studying the European methods of health service that in comparison with the United States mortality and morbidity records, European countries do not have any

marvelous records of achievement. European methods are not the answer to our health needs. We must insist on that in the formulation of these group plans. These plans do not produce better medical care but cheaper and poorer medical care. We must convince the political, health, and social welfare groups that medical care comes from individual medical attention and that the doctor's office is the best place to produce better medical care for the people. We must constantly emphasize better medical care and preventive medicine, and the pediatrician can demonstrate this best.

Our responsibilities as the New Jersey members of the American Academy of Pediatrics are (1) to the pediatricians themselves, (2) to the state society, (3) to the state department of health, and (4) to the public.

We should not forget that our *first* object is improvement of child health through periodic supervision and adequate pediatric knowledge. We should lead the way in the rehabilitation of the family physician for service to mothers, infants, and children of the preschool and school ages.

The committee is working on an outline of preventive methods for child supervision. Physicians are being appointed to hold parental conferences in "Baby Keep-Well Stations." This work is being done with social security funds.

The Public Health Hour has been recently modified by the welfare committee. The indigents will be cared for in the Public Health Hour, but the physician is not obligated in any way to do this as free service. He may refer such patients back to the public clinics if he desires. The state department will furnish free toxoid for all patients whether indigent or not. The only requirement is that the doctor report promptly (on the form required) the name and address of the patients he immunizes and vaccinates. The toxoid is not limited to indigent; it is to be free to all.

The future of pediatric practice will have to be settled on the basis of economic levels of income.

1. The low wage group we will take care of as we do now.

2. For the midde class group, we will devise a system of adjusting fees.

Dr. Hilton S. Read, the second speaker on the subject, emphasized the fact that it is the "politicalization" of medicine that we fear and in order to avoid this we must show the government that the profession is willing and able to care for the American people in an American way. The pediatricians must preserve this right to practice along the American trend. The pediatrician is the best qualified to advise on preventive medicine. We must have a united effort in the distribution of medical care and the cost thereof.

Dr. Julius Levy, the third speaker on this topic, stated that we must forget we are individuals and also think as a group. As individuals, our responsibility is merely to give the best service we can. As a group, it is our definite responsibility to give the full value of our knowledge as pediatricians and make this knowledge available to the rest of the physicians. This knowledge must be given to the people as well. No matter how extensive your practice is, you are not going to reach all the babies born during the year. The pediatric group has the opportunity to concern itself in a constructive way with problems with which the members are best fitted to deal and with what the public departments are forced to deal. The pediatricians should study prenatal deportment, high death rates from premature births, feeding, and should do more than pass resolutions. The physicians of New Jersey have a splendid opportunity to work out their own problems. No other state has such coordination between the public and private agencies, and each is willing to be guided by the other.

Dr. Wilkes announced that the annual meeting of the state society would be held in Atlantic City, April 27-29, 1937. This is earlier than usual because the American Medical Association meets in Atlantic City the first week in June.

Dr. Chester R. Brown urged that every man should take advantage of the opportunity to attend the state meeting. The spring meeting of the Academy will be held at that time, and every man should attend because he is sure to find something of interest.

Dr. L. Charles Rosenberg suggested that every man come to the spring meeting prepared to discuss the problems which he meets in everyday practice. A questionnaire could be sent out to the members on which they could write their problems. The problems could be classified and an entire day could be spent discussing these problems. Or, certain problems could be assigned to certain men and they could come to the meeting prepared to lecture on them.

Dr. Harrold A. Murray acknowledged the help given to his committee in formulating the child health lectures by Professor Light, of Rutgers, Dr. Satchwell, and Dr. Wilkes, and stated that with the help of organized medicine it has been easier to work.

Dr. London explained that Middlesex County was not opposing what the state society and the Academy are doing, but is working out a definite method for handling its peculiar situation. They hope that their method may be an example for other counties and may solve the problem of medical care for all classes of people. Their prime objective is to give the best medical care in the doctor's office at a cost which each can afford to pay.

LeRoy A. Wilkes, M.D., Secretary.
Edith L. Soden, Acting Secretary.

# Academy News

The preliminary announcement of the program for the seventh annual meeting of the American Academy of Pediatrics, to be held June 3, 4, and 5, 1937, at the Waldorf-Astoria Hotel, New York, N. Y., is as follows:

PROGRAM

*Thursday, June 3, 9:30 A.M. Round Table Discussions*

| Title | Leader |
|---|---|
| Anemia of the Newborn. | Hugh W. Josephs, M.D., Baltimore, Md. |
| Asthma. | Bret Ratner, M.D., New York, N. Y. |
| Childhood Psychiatry. | James S. Plant, M.D., Newark, N. J. |
| Common Skin Diseases. | A. Benson Cannon, M.D., New York, N. Y. |
| Diabetes. | Elliott Proctor Joslin, M.D., Boston, Mass. |
| Eczema. | Lewis Webb Hill, M.D., Boston, Mass. |
| Gonococcus Infection. | Richard W. TeLinde, M.D., Baltimore, Md. |
| Meningococcic Meningitis. | Archibald L. Hoyne, M.D., Chicago, Ill. |
| Nephritis. | John D. Lyttle, M.D., New York, N. Y. |
| Poliomyelitis. | John A. Toomey, M.D., Cleveland, Ohio. |
| Sedimentation Rate. | Thomas Duckett Jones, M.D., Boston, Mass. |
| Speech Defects. | Smiley Blanton, M.D., Ithaca, N. Y. |
| Treatment of Empyema. | Edward Donovan, M.D., New York, N. Y. |
| Vitamin. | H. C. Sherman, M.D., New York, N. Y. |

Fellows are requested to submit to the Secretary at once their choices for assignment to these round table discussions.

*Thursday, June 3, 2 P.M. Exhibit Demonstrations**

| | |
|---|---|
| Urinary Infections. | Henry F. Helmholz, M.D., Rochester, Minn. |
| Intravenous Therapy. | Alexis F. Hartmann, M.D., St. Louis, Mo. |
| Pneumonia. | Charles Hendee Smith, M.D., New York, N. Y. |

*Friday, June 4, 9:30 A.M. General Meeting*

President's Address

Scientific Papers

| | |
|---|---|
| Hypoglycemia in Infancy and Childhood. | Alexis F. Hartmann, M.D., St. Louis, Mo. |
| Diverse Attributes of Healthy Children. A Report of Progress in Understanding the "Normal Child." | Alfred H. Washburn, M.D., Denver, Colo. |

Consideration of Reports

(Reports will be presented in mimeograph form to the membership.)

Report of the executive board
Report of the secretary-treasurer
Report of regional committees
Report of special committees
New business
Installation of new president

*An attempt to bring before a large group in demonstrable form what one might see in a scientific exhibit on a special subject. Questions from the floor will be welcomed.

*Friday, June 4, 2 P.M. Panel Discussions*

Present Status of Active Immunization Against Scarlet Fever.
Chairman: Ralph S. Muckenfuss, M.D., New York, N. Y.
Present Status of Active Immunization Against Whooping Cough.
Chairman: Rustin McIntosh, M.D., New York, N. Y.

*Saturday, June 5, 9:30 A.M.*

Round table discussions will be repeated.

The Waldorf-Astoria Hotel has announced the following hotel accommodations:

Guest Room Rates.—During the period of the convention the following special schedule of rates will apply:

| | | | |
|---|---|---|---|
| Single rooms (with bath) | $4.50 | $5.25 | $6.00 |
| Twin-bedded rooms (with bath) | 7.00 | 7.50 | 8.25 |

Following the annual meeting of the Academy an unofficial cruise to Bermuda has been arranged. For information, reservations, or other matters pertaining to the cruise, address Leon V. Arnold, 36 Washington Square, W., New York, N. Y.

The following commercial exhibits will be held:

American Hospital Supply Corporation, Chicago, Ill.
American Research Products, Inc., Minneapolis, Minn.
Arch Corrector Corporation, Brooklyn, N. Y.
Arlington Chemical Company, Yonkers, N. Y.
Borden Company, New York, N. Y.
Burroughs Wellcome & Company, New York, N. Y.
Carnation Milk Sales Company, Oconomowoc, Wis.
Duke Laboratories, Inc., Long Island City, N. Y.
Foley Manufacturing Company, Minneapolis, Minn.
Gerber Products Company, Fremont, Mich.
Hanovia Chemical and Manufacturing Co., Newark, N. J.
H. J. Heinz Company, Pittsburgh, Pa.
Irradiated Evaporated Milk Institute, Chicago, Ill.
Juvenile Wood Products, Inc., Fort Wayne, Ind.
Kalak Water Company, New York, N. Y.
Lederle Laboratories, New York, N. Y.
Libby, McNeill & Libby, Chicago, Ill.
Mead Johnson & Company, Evansville, Ind.
Mellins Food Company, Boston, Mass.
The C. V. Mosby Company, St. Louis, Mo.
M & R Dietetic Laboratories, Inc., Columbus, Ohio.
National Live Stock & Meat Board, Chicago, Ill.
Nestlé's Milk Products, Inc., New York, N. Y.
E. L. Patch Company, Stoneham, Mass.
Pet Milk Company, St. Louis, Mo.
W. F. Prior Company, Inc., Hagerstown, Md.
Ralston Purina Company, St. Louis, Mo.
Scientific Sugars Company, Columbus, Ind.
S.M.A. Corporation, Cleveland, Ohio.
E. R. Squibb & Sons, New York, N. Y.
Vegex, Inc., New York, N. Y.
Myron L. Walker Co., Inc., Mount Vernon, N. Y.
White Laboratories, Inc., Newark, N. J.
Wisconsin Alumni Research Foundation, Madison, Wisconsin

The name of Dr. Irving Le Belle, 825 West End Avenue, New York, N. Y., should have been included in the list of candidates who were acted on favorably by the executive board at the fall meeting.

# News and Notes

The **Second International Congress for the Protection of Infancy** will be held in Rome, October 4-8, 1937, following the International Pediatrics Congress.

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The **American Pediatric Society** will meet for its forty-ninth annual meeting at the Homstead, Hot Springs, Virginia, on April 29, 30, and May 1, 1937. Dr. Henry F. Helmholz, Rochester, Minn., is president. Dr. Hugh McCulloch, 325 North Euclid Avenue, St. Louis, Mo., is secretary. (Please note the change in the place of meeting.)

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The **Society for Pediatric Research** will meet at Atlantic City, N. J., May 4, 1937. Headquarters will be at the Chalfonte-Haddon Hall. Dr. A. A. Weech, 630 W. 168th Street, New York, N. Y., is secretary.

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The **Section on Pediatrics of the American Medical Association** will meet at the time of the American Medical Association convention in Atlantic City on June 9, 10, 11, 1937. Dr. Ralph M. Tyson is chairman of the section. Dr. Albert D. Kaiser, 16 N. Goodman Street, Rochester, N. Y., is secretary. This meeting follows immediately the meeting of the Academy in New York the end of the preceding week.

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A postgraduate course of instruction in diseases of children will be held at the Children's Free Hospital in Louisville, Ky., beginning Wednesday, April 28, 1937, and continuing each Wednesday for ten weeks. Inquiries should be sent to Dr. Philip F. Barbour, Heyburn Building, Louisville. This course is given under the auspices of the committee on postgraduate courses in diseases of children of the Kentucky State Medical Association.

# Correspondence

London, England
February, 1937.

## VI

Comment has previously been made in these letters on the question of nutrition of children in this country, which is naturally a source of considerable public interest. It is probably worth while following this up with further reports which have come to hand during the past year.

The report of the Chief Medical Officer of the Board of Education for 1935, recently published, goes to show that reports from school medical officers throughout the country do not suggest that the nutrition of school children has on the whole deteriorated. This may be considered satisfactory, although general improvement must undoubtedly be aimed at.

The London County Council, in order to deal still more satisfactorily with the problem of undernutrition, have now set up certain "nutrition centres," the object of which is to investigate and assist cases of malnutrition in their earliest stages; the organisation of such centres is a new departure which should prove of great value.

In the annual report on medical inspection and treatment of school children in Glasgow, summarised in the *British Medical Journal* early in 1936, it is stated that the heights and weights in nearly every age group were greater than any recorded during the past fifteen years, and that the figures relating to the average nutritional condition of the children were the best recorded since 1919.

The interest aroused in physical education and training has continued. The committee set up by the Council of the British Medical Association to examine the position of physical education from the point of view of the improvement of national health and physique issued a comprehensive report which appeared in the *British Medical Journal* in April, 1936. It includes a survey of the training of teachers and leaders and devotes a section to physical culture for those no longer attending school. The Board of Education itself takes the view that physical education is an essential part of general education and is not merely one more subject that should be squeezed into the curriculum. Recent governmental action has made it quite clear that official efforts are to be made to put into force schemes for promoting physical well-being and that such efforts are regarded as having a most important bearing upon the state of nutritional health and well-being of the community.

In connexion with the consumption of milk in schools, two points of interest appear to call for comment. The first is the small extent to which milk is normally drunk by children of school age, at any rate in certain districts. A recently reported survey covering nearly 14,000 school children in Ayrshire, Scotland (which includes Glasgow), showed that one-half of the children drank no milk whatever, and of the other half roughly two-thirds took it once a day only. The second point is that, as a result of an inquiry carried out among school children in Cardiff by Dr. D. A. Williams (*British Medical Journal*, November 28, 1936), he considers that 82.7 per cent of 150 children appeared allergic to milk; he feels that, in the case of those children who exhibit a disinclination or refusal to take milk, such behaviour is probably protective in nature and that milk should not be forced on such children.

Towards the end of last year a joint committee of the British Paediatric Association and the Children's Section of the Royal Society of Medicine was set up for

the purpose of formulating a standard of prematurity. The Committee's report, which contains the following recommendation: "An immature or premature infant is one whose birth weight is 5½ pounds or less, regardless of the supposed period of gestation," has just been approved and adopted by the Council of the Royal Society of Medicine.

The British Paediatric Association is to meet at Windermere on the 7th. and 8th. of May, Dr. Leonard Findlay being this year's president.

It is impossible to close this letter without a reference to the death of Dr. W. McKim Marriott. The news of this came as a great blow to his friends and former pupils in this country, to whom it seems tragic that such a figure should be taken at so early an age. His memory will live long with us, not only on account of his contributions to paediatrics, commented upon in an obituary notice which appeared in the *British Medical Journal*, but also because of the recollection of his kindness, helpfulness, and vivid personality.

KENNETH H. TALLERMAN.

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## Errata

In the article, "Placental Immunity," by Samuel Karelitz, M.D., Charles K. Greenwald, and A. J. Klein, New York, N. Y., in the February issue of the JOURNAL, the sentence beginning the middle of line 17, page 175, should read: "If in the case of this placental globulin extract ("A") 1 c.c. contains 0.3 unit of diphtheria antitoxin and the corresponding immune serum ("B") contains 0.1 unit per cubic centimeter, we would calculate the dosage of the placental globulin extract as follows: ($x$ is the dosage sought)."

Also on page 179, line 3, the sentence should read: "$A$ is the D.A. titer of 1 c.c. of the globulin extract and $B$ the D.A. titer of 1 c.c. placental fluid."

# Comments

## THE SERUM TREATMENT OF POLIOMYELITIS

IN 1910 Levaditi and Landsteiner[1] effected, in vitro, the neutralization of the virus of poliomyelitis by means of convalescent monkey serum. This finding was quickly confirmed and extended by other workers. Obviously, serum treatment demanded a trial in man and it was not long before convalescent serum became popular with layman and physician.

In the decade of 1915 to 1925 the mortality of acute anterior poliomyelitis was generally held to range between 15 and 25 per cent. Naturally, in 1927, when Aycock and Luther[2] used convalescent serum vigorously and reported a series of 106 treated cases with but one death, most physicians felt that the value of the treatment was established. A contributing reason for optimism might have been the fact that the value of convalescent and adult serums in the prophylaxis of measles was becoming recognized. The results, indeed, were so gratifying that most people held it inadvisable to ask for a control group of untreated cases of poliomyelitis. However, the mortality was higher in the next series of treated cases reported by Aycock and his collaborators in 1929,[3] and by this time the great limitations of the serologic inactivation in vivo of many viruses were being realized.[4] Accordingly, in the epidemic of 1931, in New York, Brooklyn, and Hartford, physicians felt justified in including untreated control groups.[5, 6, 7] Certain commentators[6] felt that some untreated control groups included, by chance, a disproportionally large number of mild cases. However, prognosis in poliomyelitis is impossible, until the disease is over, and the general results in all groups pointed in the same direction, namely, that there was not much to be gained by serotheraphy. Indeed, Park[5b] found that the use of certain serum greatly increased the mortality (refined horse serum given intraspinously).

Since 1920 there has been a widening interest in virus diseases in general, since 1930 in neurotropic viruses in particular, and by the generosity of many people great funds have been made available for the study of poliomyelitis. Accordingly projects, impracticable to earlier workers, have been carried out in the last few years. The accumulating mass of new data indicates that it is futile to expect any practical value from serotherapy. The new pertinent findings lie in the fields of epidemiology, histology, experimental pathology, and immunology, and they may be summarized as follows: mild nonparalytic attacks of the disease are usual and extremely common; so common in certain epidemics as almost to rival measles in frequency.[8, 9] The answer to important epidemiologic and therapeutic questions is dependent upon a full knowledge and recognition of the clinical picture and course of that ill-defined, but very common, entity, the nonparalytic case, as well as a knowledge as to what the ratio of untreated nonparalytic cases to untreated paralytic cases would be, *in any given epidemic.* Unfortunately, the statement of Wickman, who first adequately described abortive (nonparalytic) poliomyelitis more than twenty-five years ago, still holds, namely, that, although abortive types make up a considerable proportion of all the cases in any epidemic, "their exact ratio we cannot yet determine." But it is clear that in recent epidemics such abortive or nonparalytic cases outnumber the paralytic cases by many times and are much more frequent than many realize. A situation of this kind can easily furnish "brilliant" results when any treatment is given early, and so it demands the most rigid group of control patients who are untreated, if a satisfactory opinion is to be reached.

These mild attacks generally occur without demonstrable changes in the spinal fluid, and sometimes cases with paralysis occur with normal spinal fluid.[10, 11] This is in harmony with the fact that in experimental poliomyelitis the virus does not spread via meninges or spinal fluid but produces lesions in, and is spreading through, neurons coincidently with, if not before, the first general symptoms.[12, 13, 14] Accordingly, the notion proposed by Draper,[15] that the "dromedary" phenomenon speaks for a constitutional and a neurologic localization of virus, is probably inadequate. Most likely in the "preparalytic" stage in man the virus has already attacked nerve cells. Therefore, one cannot expect to modify the disease by means of serotherapy at this time because antibody does not modify virus after it has attacked susceptible cells.[16]

In experimental infection in monkeys it has been impossible to demonstrate any value for serotherapy and has been difficult to show that passive protection lasts for a day or two.[17-20] In vitro neutralization of virus by immune serum continues to be demonstrable with considerable regularity, and by this means it has been shown that there are serologically distinct races of the virus.[21, 22, 23] This heterogenicity of races of virus casts still more doubt on the efficacy of convalescent serum in poliomyelitis. More important than this is the fact that in all other virus diseases of the central nervous system; whether tried in the natural or the experimental host, serum *treatment* is ineffective, although in vitro neutralization and often active immunization are possible. This list includes Borna disease, louping-ill, rabies, mad itch, St. Louis encephalitis, vaccinal encephalitis, herpes encephalitis, and others.*

Recently, however, the subject of serum treatment in poliomyelitis has been reopened by Harmon[24] and by an editorial in the *Journal of the American Medical Association*, Aug. 8, 1936. The new evidence consists in the citation of three favorable series of treated cases: Cowie and his coworkers[25] in Michigan, Jensen,[26] in Denmark, and Levinson,[27] in Chicago. Not one of the series was satisfactorily controlled, and in a criticism of the editorial, Fischer[28] cited a series of mild untreated cases in the epidemic of the summer of 1935 in New York City. There were 282 "preparalytic" cases of poliomyelitis admitted to the Willard Parker Hospital. None received serum or transfusion; there was one death† and the incidence of paralysis was 20 per cent. This is the most successful series on record; the treatment was bed rest.

To summarize, one might say that from 1910 to 1930 various types of serotherapy in poliomyelitis have seemed logical according to the current views of experimental pathology. In 1927 convalescent serum therapy seemed established because, by chance, large numbers of mild forms of the disease were included in an important study, which at that stage of knowledge had to be uncontrolled. Since 1931 controlled studies have shown that serum treatment has little or no value and advances in experimental pathology have demonstrated there is now no valid reason to believe serum treatment could have succeeded and every reason to believe it will continue to fail unless some new fundamental discovery in the future provides a method of modifying the union of virus and susceptible cell.

Although it may appear to be a little beside the point, one may conclude these remarks by pointing out that the actual efficacy of any serum in the treatment of acute poliomyelitis is often not the real deciding factor as to whether or not a

*Serum treatment has proved ineffective in all virus diseases in which it has been tried. One now apparent exception may or may not prove to be a true one. It is the description by Laidlaw, Smith, Andrewes, and Dunkin: (Brit. J. Exper. Path. 16: 275, 1935) of an antiserum in experimental influenza.

†If the reference[28] is consulted, the reader will note that the mortality recorded for the 282 cases is zero. However, Dr. Fischer, in replying to a recent query on this point, wrote confirming the general tenor of the citation but stated that a recheck of the records revealed one death among the 282 "preparalytic" cases. He added that all patients included in the series had diagnostic lumbar punctures.

(See also Fischer, E. A., and Stillerman, M.: Am. J. Dis. Child. In Press).

child is given such treatment during an epidemic of poliomyelitis. The deciding factor is very often the pressure brought to bear by the public. For the use of serum in poliomyelitis has been so publicized and the fear of the disease (both by laymen and physicians) is so great, that many physicians, in this country at least, hesitate to "withhold" serum treatment. This attitude, which may at first seem to be questionable, is a natural outcome of the present situation. Inasmuch as the public has been repeatedly told that there is a "serum for the disease" and inasmuch as it has apparently been difficult to judge whether such treatment is effective or not, how much more difficult must it be for a few lone members of the profession to stand out against what seems to be an overwhelming "official" opinion and an overwhelming popular demand. In our experience, for example, it is usual to hear a physician, who is quite cognizant of the recent literature on the subject, maintain that "whether the serum does any good or not, if my child had any suspicion of early poliomyelitis, I would immediately administer serum."

In this discussion several sweeping statements have been made. They might be conditioned by supplementary factors which have been considered at some length in Harmon's critical review,[24] to which the reader is referred, but in the last analysis we must recognize that the conclusion that "serum" is valueless has been reached in the clinical field by those who have observed the most important rule in this type of study, namely, they have studied patients untreated with serum. If we accept these conclusions, we should go one step farther and consider another aspect of the problem which is not often raised. That is, if it is shown that the administration of serum does no good, may it do harm? To this question no satisfactory answer can be given. Practically there is no conclusive evidence that it does harm if properly prepared serum is properly administered, but theoretically a child with early poliomyelitis who is hanging in the balance between the development of paralysis or no paralysis should hardly be subjected to a valueless procedure, which involves the injection of protein, even though reactions are unlikely to occur.

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